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Keywords:	resection, radiofrequency ablation, microwave ablation, transcatheter arterial chemoembolization, percutaneous ethanol injection, hepatocellular carcinoma

Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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List of abbreviations in order of appearance: HCC: hepatocellular carcinoma; RES: resection; RFA: radiofrequency ablation; MWA: microwave ablation; TACE: transcatheter arterial chemoembolization; PEI: percutaneous ethanol injection; GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TR: TACE plus RFA; OS: overall survival; MCMC: Markov Chain Monte Carlo; CrI: credible interval; SUCRA: surface under the cumulative ranking curve LPS: lipopolysaccharide; TNFα: tumor necrosis factor α; IL: interleukin; TGFβ: transforming growth factor β.

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Abstract

Objective: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

Methods and analyses: We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

Results: We identified 62 studies, including 23893 patients. After adjustment for study design, and in the full sample of studies, the treatments were ranked as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI. The ranks were similar for 1 and 3-year survival, with RES and TR being the highest ranking treatments. In both smaller (<3cm) and larger tumors (3-5cm), RES and TR were also the two highest ranking treatments. There was little evidence of inconsistency between direct and indirect evidence.

Conclusion: The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival. However, many of the between-treatment comparisons were not statistically significant and, for now, selection of strategies for treatment will depend patient and disease characteristics. Additionally, much of the evidence was provided by non randomised studies and knowledge gaps still exist.

More head-to-head comparisons between both RES and TR, or other approaches, will be necessary to confirm these findings.

Key words: resection; radiofrequency ablation; microwave ablation; transcatheter arterial chemoembolization; percutaneous ethanol injection; hepatocellular carcinoma.

Strengths and limitations of this study:

1. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

2. We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

3. The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival.

4. A major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival.

5. All included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies.

Introduction

Cancer was the second leading cause of death in 2013, behind cardiovascular disease, and in 2013 more than 8 million people died from cancer globally [1-3]. Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and the 3rd leading cause of cancer death, with 5-year overall survival rates under 12% [4 5].

Hepatic resection (RES) is the traditional choice for patients with HCC, without cirrhosis and with good remaining liver function [6]. Despite nearly 70% 5-year survival, recurrence rates with surgery are high [7]. Repeated hepatectomies to lengthen survival are not often appropriate owing to multiple-site tumor recurrence or patient background of liver cirrhosis [8 9]. Many locoregional therapies have been developed including ablative treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), or microwave ablation (MWA), and trans-arterial therapies such as transcatheter arterial chemoembolization (TACE) or transarterial chemotherapy infusion (TACI). Locoregional therapies are minimally invasive and therefore are cheaper and faster to recover from, as compared to resection. Such approaches may be appropriate for patients with unresectable, small or multiple carcinomas or those with severe cirrhosis. However, there may be a greater risk of recurrence because of incomplete destruction of cancer cells at the treatment margin, as seen with RFA [10].

Selection of treatment strategy is determined by liver function, tumour stage and patient performance status [7], but much uncertainty still remains surrounding the comparative efficacy of different treatment approahces. A recent review of international guidelines for HCC found similarities but also some discrepancy in treatment allocation recommendations because of regional classification differences, secondary to a lack of solid or high-level evidence [11]. A recent review of therapies also revealed that there was no consensus on whether surgery or ablation was better for small tumors [7]. Some discrepancy in prevalence and treatment outcomes may remain in different regions because of local biology, available resources or expertise and access to care [11]. However, if we ever hope to achieve standardized and evidence-based therapy for HCC, the unanswered question surrounding relative treatment efficacy of RES compared to ablative locoregional therapies must be resolved.

Traditional meta-analysis is limited by existing head-to-head treatment comparisons within included studies. It is therefore not possible to gauge the relative benefit of two treatments that have never been directly compared in studies. Real-life treatment-decisions are hindered by gaps in existing evidence, but network meta-analysis enables integration of direct and indirect comparisons to provide estimates for relative comparisons across many treatments [12]. In order to investigate comparative effectiveness among RES and common locoregional ablative therapies, we performed a systematic review and network meta-analysis.

Search Strategy

We conducted a systematic review and report findings in accordance with PRISMA for Network Meta-Analyses (PRISMA-NMA) [13] (PRISMA NMA Checklist).

The following databases were searched: PubMed, Embase, Web of science and Scopus, up to December 2015, using these keywords: resection, surgery, hepatectomy, radiofrequency ablation, transarterial chemoembolization, microwave thermal ablation, ethanol injection, liver, cancer, tumor (Additional file 1: Text S1). No language restrictions were used. Bibliographies from other relevant review articles were cross-examined for potential missed studies. Disagreement was resolved by a third reviewer. Citations were downloaded into reference management software and duplicate citations were electronically or manually removed.

We systematically included the studies using the following criteria: 1) original data from prospective or retrospective cohort studies and randomized clinical trials (RCTs) in humans; 2) reporting at least two treatments, including resection or any local ablative therapy (RES, RFA, MWA, PEI, or TACE+RFA (TR)); 3) mean lesion size ≤ 5 cm; 4) evaluating overall survival rate not less than one year after first or recurrent treatments. Conference abstracts and case reports were excluded, as were older publications from studies with multiple publications. Studies were excluded where particpants had received combinations of the 5 included treatment approaches, such that outcomes could not be ascribed to individual therapies.

Data Extraction and Study Quality

Two investigators independently extracted and cross-checked the data from the eligible studies: author, year, study design, country, disease type, inclusion criteria, treatment style, study size, gender, age, tumor size, follow-up duration, treatment complications and survival outcomes. If in disagreement, a third reviewer adjudicated. The level of evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance [14], which was classified into four levels of high, moderate, low, and very low. The quality score was downgraded according to 5 domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias while scores were upgraded according to large effect, appropriate control for plausible confounding, and dose-response gradient.

Data Analysis

Network meta-analysis was used if a closed evidence loop was available. When possible, pair-wise direct head-to-head comparisons were conducted to calculate the pooled odds ratio (OR) and its 95% confidence interval (CI). Between-study heterogeneity was evaluated using the tau-squared statistic (τ^2) [15]. A node-splitting analysis was applied to check the consistency between direct evidence (existing real reported comparisons) and indirect evidence (estimated treatment comparisons) for their agreement on a specific node [16]. Bayesian network meta-analysis with Markov Chain Monte Carlo (MCMC), through a consistency model, was utilized to estimate the pooled ORs and its 95% credible interval (CrI) for the direct and indirect comparisons. The inconsistency model was used to check for heterogeneity due to chance imbalance in the distribution of effect modifiers. Consistency in every closed loop was checked by the loop-specific approach in order to estimate whether treatment survival effects were disturbed by variance in the distribution of potential confounding factors among the studies. In order to compare and rank survival rates of different treatments we examined all studies first and then separately assessed smaller (<3cm) and larger (3-5cm) tumors. Random-effect meta-regression models were used, with and without adjustment for study design (cohort or RCT) and subgroup analyses were also conducted for RCTs in order to examine treatment effectiveness. We appraised the ranking probabilities for all therapies for each intervention and the treatment hierarchy was ordered by the surface under the cumulative ranking curve (SUCRA) [17]. Sensitivity analysis was conducted to remove each study, in turn, and estimate the treatment effect in the remaining studies. Funnel plots were utilized to check the possible presence of publication bias or small-study bias [18]. In this study, we used Bayesian MCMC simulations by WinBUGS 1.4 and graphically presented the results using Stata 13.

Results

Study Characteristics

After screening, 62 relevant studies in 61 articles were identified, of which 18 were randomized controlled trials and 44 were cohort studies [19-80]. We excluded 61571 duplicate or non-relevant citations (Figure 1). The summary characteristics of these studies are shown in Additional file 1: Table S1. Overall, 23893 patients of mean age from 46 to 73.5 years, with approximately 29236 tumors, were assigned to receive RES, RFA, MWA, TR and PEI, and the mean follow-up ranged from 1.5 to

5.7 years.

Network Meta-Analysis Results

Ten possible treatment comparisons among the five interventions were examined in the included studies. Comparable survival estimates were made for each treatment (per 1000 patients) and the survival OR among each of the treatment comparisons, according to follow-up duration, are presented in Additional file 1: Table S2, along with estimation of the quality of evidence using GRADE criteria.

Across the range of treatment comparisons and follow-up durations, evidence was graded between low and high quality. Evidence was often graded as low quality owing to publication bias and graded as high quality owing to a larger number of participants in direct comparisons.

Survival probabilities (estimated using Meanrank) and ranks for the five treatments in patients with tumours <3cm, 3-5cm or ≤5cm (with and without adjustment for study design) are graphically displayed in Figures 2-5, and numerical details are given in Additional file 1: Table S3-S4. RES was consistently associated with greater survival (rank 1) compared to MWA, RFA, TR and PEI for the 5-year survival estimates. The ranks were similar for 1 and 3-year survival with RES or TR being ranked as 1 or 2 in most analyses. After adjustment for study design, and in the full sample of available studies (n=40), the treatments were ranked as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI (Table S4).

Efficacy comparisons from network meta-regression for all treatments are summarized in Table 1 and 2, according to follow-up duration and initial tumor size. Compared to RES, 5-year survival in all studies (trials and observational studies) for all tumours ≤5cm, estimated from network comparisons, was 0.47 (95%CrI 0.22 to 0.87) for PEI, 0.79 (95%CrI 0.24 to 1.92) for TR, 0.56 (95%CrI 0.23 to 1.14) for MWA and 0.56 (95%CrI 0.27 to 0.99) for RFA (Table 2). When examining the comparisons across all treatments, the only significant difference for tumours <3cm was for 5-year survival, and a significantly worse survival was observed for PEI compared to RES 0.46 (95%CrI 0.18 to 0.95). For tumours between 3 and 5 cm, no significant differences were observed at 5-year survival, but significantly worse 3-year survival was observed with PEI, MWA and RFA compared to RES (Table 2). Despite smaller number of studies in analyses of only RCTs, the pairwise comparisons showed similar results. However, all relative rankings should be interpreted with caution because most network meta-regression comparisons did not suggest a statistically significant difference between treatments. Detailed results of each comparison for survival rates are shown in Additional file 1: Table S5-S10**.**

Loop-specific methods detected no inconsistency between the pairwise and network meta-analysis for most closed loops in the network (Additional file 1: Figure S1). However, inconsistency was observed between direct and indirect comparisons for the following loops: lesions <3cm: RES-RFA-TR, PEI-RES-RFA, MWA-RES-RFA; lesions 3-5cm: MWA-RES-RFA, RES-RFA-TR; and lesions ≤5cm: RES-RFA-TR). In addition, tests for inconsistency were carried out (Additional file 1: Table S11-S13), which indicated a close relationship of between-trial heterogeneity and inconsistency between "direct" and "indirect" evidence.

Sensitivity Analysis and publication bias

No significant change was observed when any one study was deleted. Funnel plots indicated that the included studies in each group were distributed symmetrically around the vertical line (x=0), suggesting that no obvious evidence of publication bias or small-sample effect existed in this network (Additional file 1: Figure S2).

Discussion

There are many techniques for attaining a large ablated zone and complete necrosis of HCC and this comprehensive review addresses two of the more common treatments, namely resection and ablation. In this network meta-analysis, of the five examined therapies, the pooled data showed RES ranked best in full sample analysis with or without adjustment for study design. In both smaller (<3cm) and larger tumors (3-5cm) RES remained the highest ranking treatment. However, most of the individual treatment comparisons were not statistically significant and thus, RES may not be superior to all other therapies. Our evidence indicates locoregional therapies and particularly RES or TR (TACE+RFA) are associated with longer survival.

Our observation of better survival outcomes with TR may be through the advantage of dual mechanisms. With TR, TACE induces hypoxic injury on cancer cells through occlusion of blood vessels and is followed by local ablation. This combination therapy may result in a larger ablated zone [81], reduce the possibility of micrometastasis and recurrence, and thus, result in better survival outcomes than RFA alone.

While being more invasive, and despite risk of complications, RES was associated with better survival outcomes after 1 year, 3 years and 5 years. This may be due to removal of larger sections of liver than can be targeted with locoregional therapies, thus removing a larger area of potentially cancerous cells. Additionally, rat models indicate that the liver has the potential to quickly restore its original size after partial hepatectomy. This may be mediated via interactions of lipopolysaccharide (LPS), tumor necrosis factor (TNF)α, interleukin (IL)-6, and transforming growth factor β (TGFβ) [82]. However, evidence from rat models and human studies indicates that resection success is associated with resection size and regeneration is stunted with larger resections [83-85]. The safe limit for remnant liver volume in normal liver is approximately 30% of total liver volume, but this is estimated to rise to 40-50% in those with liver disease [83 86]. Liver resection is recognised as the mose efficient treatment for HCC but is only applicable for less than 30% of all patients (Morise 2014). However, developments in preoperative imaging tachniques, laproscopic surgery and newly developing combinations with chemotherapy may extend its application to more advanced tumors [86]. Furthermore, the consistent associations observed with all studies and only in RCTs indicates that patient selection bias in the observational studies does not wholly explain the better survival outcomes with RES.

Overall, we found PEI was associated with shorter survival than the other four therapies, a finding which is supported in previous studies [20 29]. One study reported RFA was superior to PEI in achieving short- and long-term survival outcomes, although PEI and RFA showed similar 5-year survival in lesions <3 cm [51]. The possible reason why PEI is less effective than RFA may be because lesions often have a thick capsule and therefore ethanol may not distribute through tissues.

There are several limitations in this study. Firstly, a major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival. Secondly, this study included both RCTs and observational studies, in which study designs and type of data collection may not be comparable. However, findings were consistent among both study designs. Thirdly, all included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies. Fourthly, for many individual comparisons, there were either no direct comparisons or comparisons from only a small number of studies. The lack of evidence may increase the risk of bias, which could enlarge or undervalue effect size, and may explain the small inconsistency seen between direct and estimated comparisons. Thus, we should be cautious in interpreting treatment rankings for the different survival times and for different size lesions. While adverse events from treatments may differ (not evaluated in detail in this review), by examining overall survival outcomes in our review, we have taken account of both long-term potential benefits and harms from treatments. The focus of these findings should therefore be on the overall observation that RES or TR may be superior in terms of survival, rather than focusing on specific OR values for individual treatment comparions.

In conclusion, the findings of the current bayesian network meta-analysis indicate that RES or TR may be among the most effective therapeutic approaches for HCC for 5-year survival in both smaller (< 3cm) and larger (3-5cm) lesions. However, evidence was of variable quality, and the majority of evidence came from non randomised studies, which are prone to selection bias and knowledge gaps still exist. For not, at the individual level, selection of strategies should depend on patient and clinical characteristics. To facilitate generation of evidence-based recommendations for HCC therpy, and to standardize treatment approaches, further head-to-head comparisons, especially of resection and ablative therapies, are required from high-quality RCTs, with long follow-up for survival outcomes.

Conflict of interests

The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement

No additional data are available.

Acknowledgments

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File legends:

Figure 1 Flow chart of search.

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Table 1 Odds ratios (95% credible interval) according to network meta-analyses for efficacy of treatments for all pairwise comparisons in randomized controlled trials.

〈3cm for 1-year survival

PEI				
10.75 (0.01-29.11)	TR			
0.08 (0-0.42)	1.42 (0-5.94)	MWA		
0.68 (0.28-1.36)	13.24 (0.02-55.15)	**154.8 (1.74-590.10)**	RFA	
0.68 (0.19-1.76)	15.61 (0.02-54.78)	**161.8 (1.39-581.00)**	1.01 (0.40-2.14)	RES

〈3cm for 3-year survival

PEI				
1.29 (0.13-4.99)	TR			
NA	NA	MWA		
0.88 (0.44-1.79)	1.64 (0.20-5.84)	NA	RFA	
0.75 (0.28-1.89)	1.44 (0.14-5.50)	NA	0.86 (0.40-1.68)	RES

〈3cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
0.93 (0.08-3.85)	NA	NA	RFA	
0.49 (0.04-2.02)	NA	NA	0.71 (0.10-2.47)	RES

3-5cm for 1-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.40 (0.64-11.93)	NA	RFA	
NA	1.00 (0-5.00)	NA	0.25 (0-1.47)	RES

3-5cm for 3-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.98 (0.71-15.22)	NA	RFA	
NA	1.14 (0-6.20)	NA	0.24 (0-1.25)	RES

3-5cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	7.64 (0.14-42.49)	NA	RFA	
NA	12.87 (0.02-44.43)	NA	1.05 (0.03-5.33)	RES

≤5cm for 1-year survival

PEI				
0.26 (0.06-0.69)	TR			
0.24 (0.03-0.81)	1.26 (0.14-4.73)	MWA		
0.65 (0.32-1.14)	**3.3 (1.05-8.21)**	4.62 (0.85-15.59)	RFA	
0.42 (0.14-0.98)	2.15 (0.49-6.46)	2.75 (0.52-9.18)	0.65 (0.28-1.31)	RES

≤5cm for 3-year survival

PEI				
0.49 (0.13-1.33)	TR			
1.25 (0.11-5.36)	3.25 (0.24-14.23)	MWA		
0.83 (0.39-1.73)	2.09 (0.81-4.65)	1.71 (0.17-6.61)	RFA	
0.66 (0.23-1.78)	1.69 (0.47-4.87)	1.18 (0.16-4.30)	0.80 (0.36-1.69)	RES

≤5cm for 5-year survival

PEI				
1.51 (0.02-7.71)	TR			
NA	NA	MWA		
0.90 (0.08-3.65)	3.59 (0.14-18.06)	NA	RFA	
0.49 (0.04-2.03)	2.96 (0.05-14.70)	NA	0.72 (0.11-2.48)	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

Table 2 Odds ratios (95% credible interval) according to network meta-analyses for efficacy of treatments for all pairwise comparisons in all studies

〈3cm for 1-year survival

PEI				
0.56 (0.07-2.13)	TR			
0.55 (0.18-1.29)	1.96 (0.21-7.87)	MWA		
0.69 (0.39-1.13)	2.45 (0.33-8.72)	1.51 (0.60-3.11)	RFA	
0.71 (0.24-1.60)	2.51 (0.26-9.65)	1.55 (0.41-4.10)	1.03 (0.42-2.07)	RES

〈3cm for 3-year survival

PEI				
0.59 (0.15-1.67)	TR			
1.01 (0.45-2.00)	2.35 (0.54-6.80)	MWA		
0.95 (0.59-1.47)	2.21 (0.60-5.76)	1.02 (0.54-1.76)	RFA	
0.80 (0.33-1.68)	1.87 (0.40-5.56)	0.87 (0.31-1.96)	0.85 (0.40-1.62)	RES

〈3cm for 5-year survival

PEI				
1.06 (0.19-3.41)	TR			
0.90 (0.38-1.83)	1.37 (0.23-4.59)	MWA		
0.81 (0.48-1.28)	1.24 (0.25-3.80)	1.00 (0.50-1.77)	RFA	
0.46 (0.18-0.95)	0.72 (0.11-2.48)	0.58 (0.18-1.33)	0.58 (0.24-1.11)	RES

3-5cm for 1-year survival

PEI				
0.21 (0.04-0.56)	TR			
0.60 (0.09-1.94)	3.46 (0.57-11.35)	MWA		
0.50 (0.17-1.13)	**2.92 (1.14-6.65)**	1.25 (0.31-3.46)	RFA	
0.10 (0-0.63)	0.56 (0-3.31)	0.24 (0-1.61)	0.19 (0-1.18)	RES

3-5cm for 3-year survival

PEI				
0.30 (0.03-1.06)	TR			
0.90 (0.08-3.36)	3.48 (0.62-11.64)	MWA		
0.57 (0.10-1.83)	2.37 (0.90-5.53)	1.01 (0.25-2.72)	RFA	
0.09 (0-0.44)	0.36 (0.01-1.73)	**0.15 (0-0.77)**	**0.14 (0.01-0.68)**	RES

3-5cm for 5-year survival

PEI				
6.11 (0-3.02)	TR			
1.88 (0.04-5.54)	13.88 (0.19-50.64)	MWA		
0.79 (0.05-2.64)	7.08 (0.25-26.41)	1.25 (0.18-3.84)	RFA	
1.88 (0.01-3.18)	14.49 (0.05-27.29)	1.79 (0.03-5.39)	0.91 (0.05-4.18)	RES

≤5cm for 1-year survival

PEI				
0.30 (0.11-0.63)	TR			
0.91 (0.41-1.79)	**3.51 (1.78-8.52)**	MWA		
0.78 (0.51-1.13)	**3.01 (1.33-6.15)**	0.95 (0.48-1.67)	RFA	
0.61 (0.26-1.25)	2.35 (0.74-5.96)	0.73 (0.28-1.55)	0.78 (0.37-1.49)	RES

≤5cm for 3-year survival

PEI				
0.52 (0.25-0.96)	TR			
1.03 (0.56-1.77)	2.16 (0.99-4.16)	MWA		
0.92 (0.63-1.32)	**1.93 (1.05-3.29)**	0.94 (0.58-1.44)	RFA	
0.71 (0.37-1.30)	1.50 (0.64-3.08)	0.72 (0.36-1.32)	0.78 (0.44-1.29)	RES

≤5cm for 5-year survival

PEI				
0.71 (0.26-1.57)	TR			
0.90 (0.47-1.58)	1.50 (0.52-3.46)	MWA		
0.85 (0.57-1.22)	1.42 (0.58-2.96)	1.01 (0.60-1.59)	RFA	
0.47 (0.22-0.87)	0.79 (0.24-1.92)	0.56 (0.23-1.14)	**0.56 (0.27-0.99)**	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;
RFA: radiofrequency ablation;
MWA: microwave ablation;
TR: transcatheter arterial chemoembolization and radiofrequency ablation;
PEI: percutaneous ethanol injection.

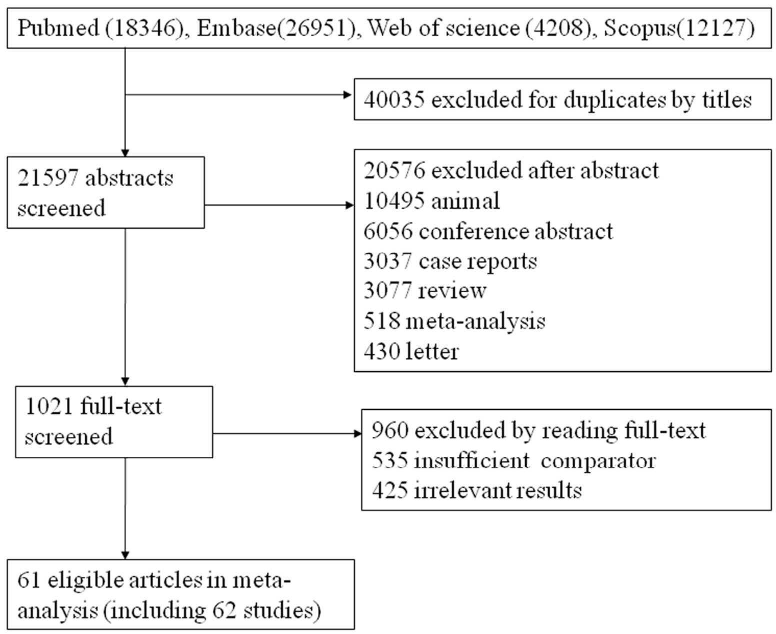

Figure 1 Flow chart of search.

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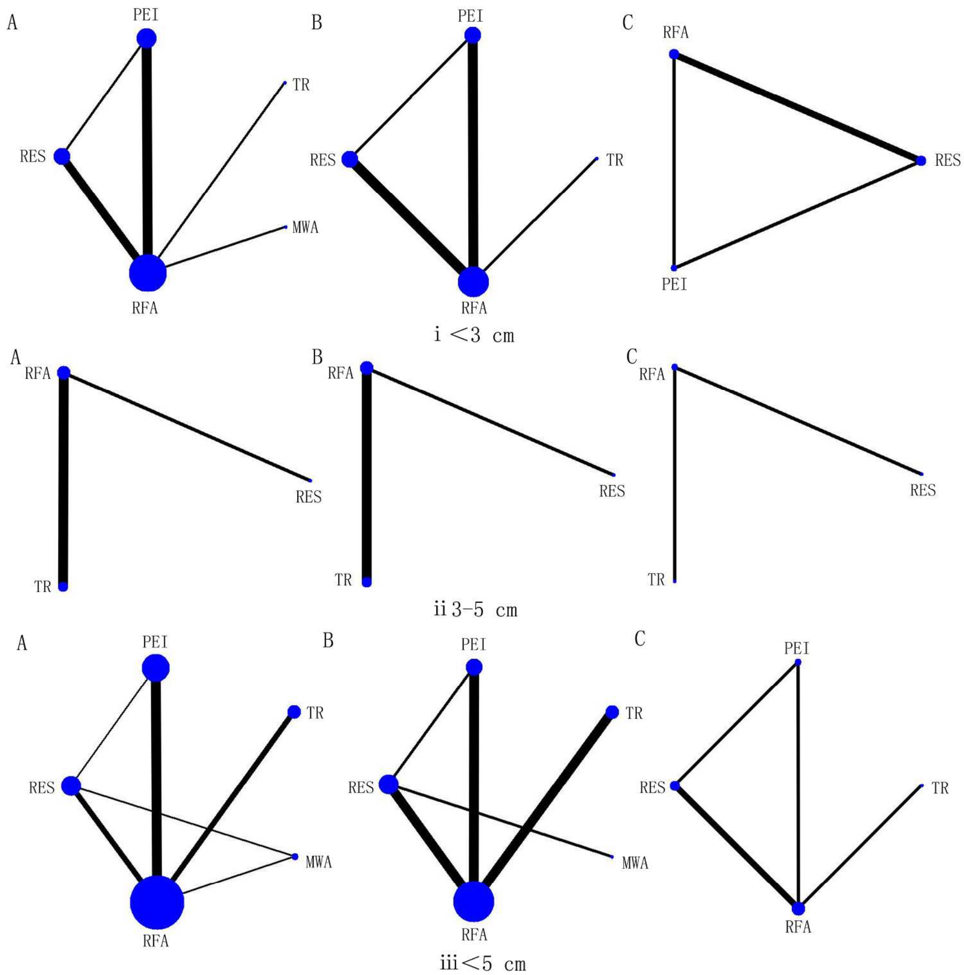

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

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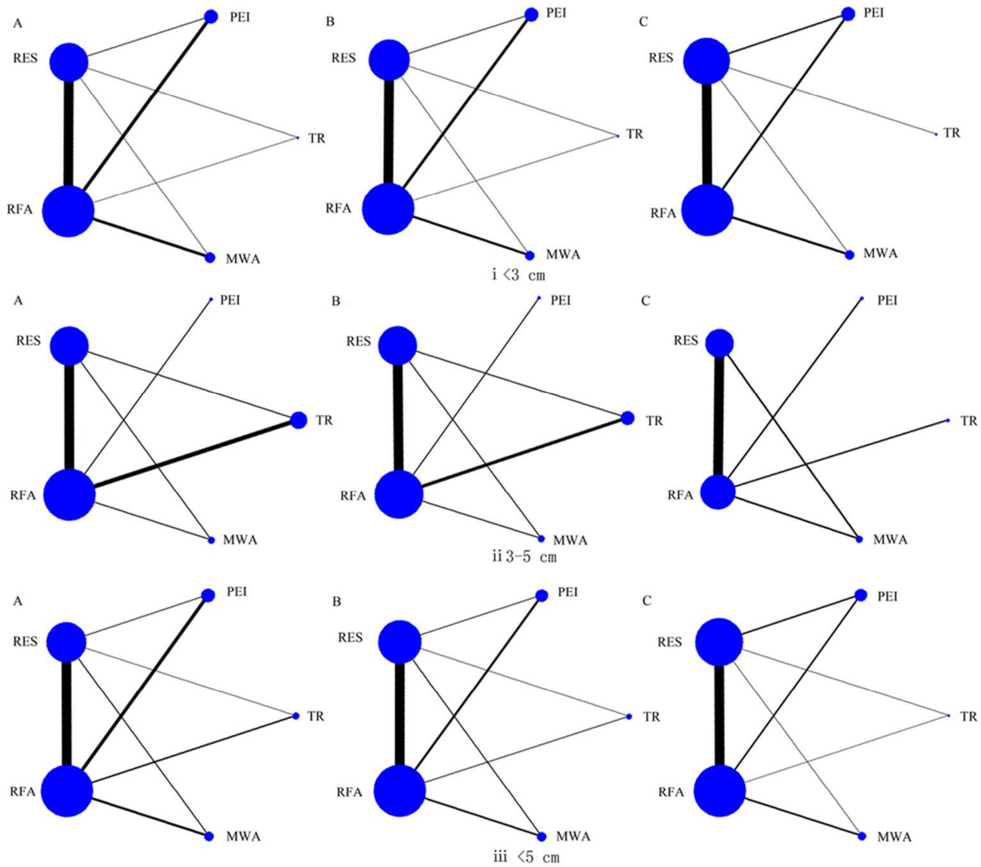

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

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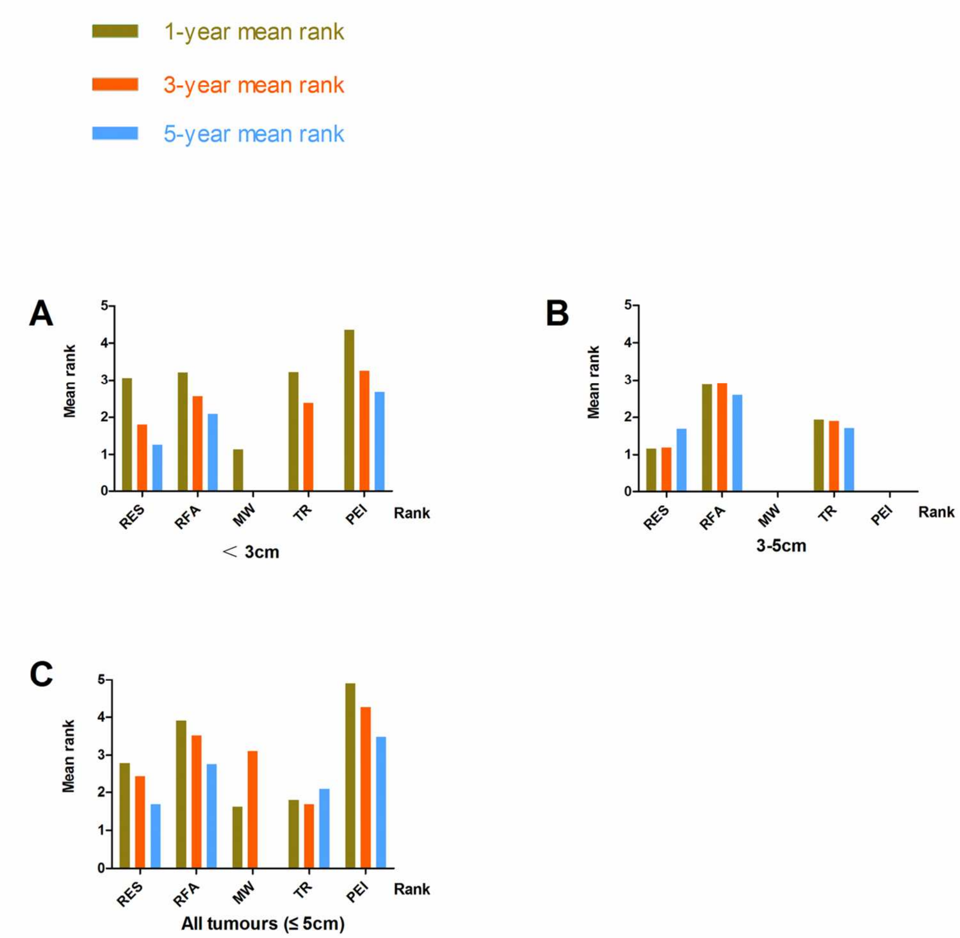


Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

118x117mm (300 x 300 DPI)

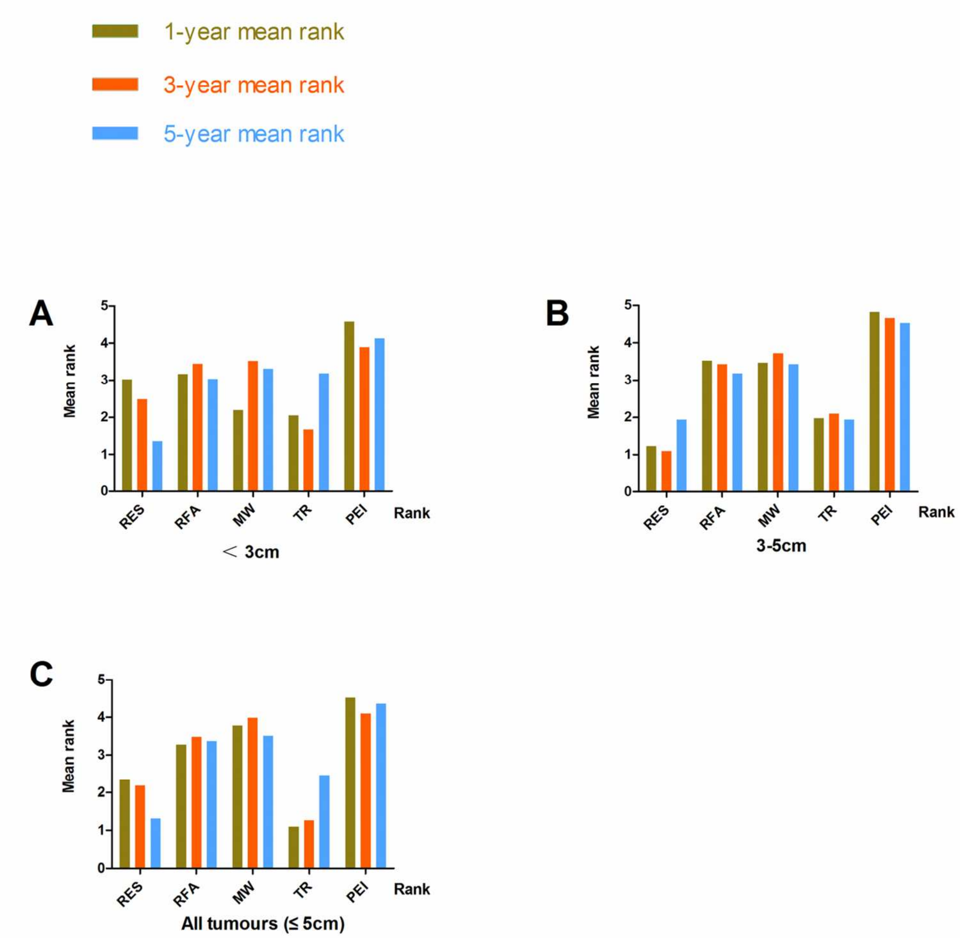


Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

118x117mm (300 x 300 DPI)

Text S1.

Search strategy:

Pubmed (1950-present)

1. ("TACE" OR "transarterial chemoembolization")
2. ("RFA" OR "radiofrequency ablation" OR "RF ablation" OR "radiofrequency thermal ablation" OR "RTA")
3. (PEI OR "ethanol injection" OR "ethanol ablation" OR "alcohol ablation")
4. ("microwave ablation" OR "microwave thermal ablation" OR MWA)
5. (liver OR hepato*)
6. (neoplas* OR cancer OR tumor OR tumour OR carcinoma OR oncolog*)
7. 1 OR 2 OR 3 OR 4
8. 5 AND 6 AND 7
9. "Ablation Techniques"[Mesh]
10. "Embolization"[Mesh]
11. "Liver Neoplasms"[Mesh]
12. 9 OR 10
13. 12 AND 11
14. 8 OR 13
15. (resection OR surgery OR hepatectomy)
16. (ablation OR injection OR embolization)
17. 5 AND 6 AND 15 AND 16
18. "Hepatectomy"[Mesh]
19. 12 AND 18 AND 11
20. 17 OR 19
21. 14 OR 20

Embase(1980-present)

1. ' TACE':ab,ti
2. ' transarterial chemoembolization':ab,ti
3. 1 OR 2
4. 'rfa':ab,ti

5. 'radiofrequency ablation':ab,ti
6. 'rf ablation':ab,ti
7. 'radiofrequency thermal ablation':ab,ti
8. 'rta':ab,ti
9. 4 OR 5 OR 6 OR 7 OR 8
10. 'PEI':ab,ti
11. ' ethanol injection ':ab,ti
12. ' ethanol ablation ':ab,ti
13. ' alcohol ablation ':ab,ti
14. 10 OR 11 OR 12 OR 13
15. ' microwave ablation ':ab,ti
16. ' microwave thermal ablation ':ab,ti
17. ' MWA ':ab,ti
18. 15 OR 16 OR 17
19. ' liver':ab,ti
20. ' hepato*':ab,ti
21. 19 OR 20
22. ' neoplas*':ab,ti
23. ' cancer ':ab,ti
24. ' tumor ':ab,ti
25. ' tumour ':ab,ti
26. ' carcinoma ':ab,ti
27. ' oncolog*':ab,ti
28. 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. 3 OR 9 OR 14 OR 18
30. 21 AND 28 AND 29
31. ' resection':ab,ti
32. ' surgery':ab,ti
33. ' hepatectomy':ab,ti
34. 31 OR 32 OR 33
35. ' ablation':ab,ti

36. ' injection':ab,ti
37. ' embolization':ab,ti
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Scoups

1. TITLE-ABS-KEY (“TACE”)
2. TITLE-ABS-KEY (“transarterial chemoembolization”)
3. 1 OR 2
4. TITLE-ABS-KEY ("RFA")
5. TITLE-ABS-KEY (“radiofrequency ablation”)
6. TITLE-ABS-KEY ("RF ablation")
7. TITLE-ABS-KEY ("radiofrequency thermal ablation")
8. TITLE-ABS-KEY ("RTA")
9. 4 OR 5 OR 6 OR 7 OR8
10. TITLE-ABS-KEY (“PEI”)
11. TITLE-ABS-KEY (“ethanol injection”)
12. TITLE-ABS-KEY (“ethanol ablation”)
13. TITLE-ABS-KEY (“alcohol ablation”)
14. 10 OR 11 OR 12 OR 13
15. TITLE-ABS-KEY ("microwave ablation")
16. TITLE-ABS-KEY ("microwave thermal ablation ")
17. TITLE-ABS-KEY ("MWA")
18. 15 OR 16 OR 17
19. TITLE-ABS-KEY ("liver ")
20. TITLE-ABS-KEY ("hepato*")
21. 19 OR 20
22. TITLE-ABS-KEY ("neoplas*")
23. TITLE-ABS-KEY ("cancer")

24. TITLE-ABS-KEY ("tumor")
25. TITLE-ABS-KEY ("tumour")
26. TITLE-ABS-KEY ("carcinoma")
27. TITLE-ABS-KEY ("oncolog*")
28. 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. 3 OR 9 OR 14 OR 18
30. 29 AND 21 AND 28
31. TITLE-ABS-KEY ("resection")
32. TITLE-ABS-KEY ("surgery")
33. TITLE-ABS-KEY ("hepatectomy")
34. 31 OR 32 OR 33
35. TITLE-ABS-KEY ("ablation")
36. TITLE-ABS-KEY ("injection")
37. TITLE-ABS-KEY ("embolization")
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Web of science

1. TS=(ablation)
2. TS=(embolization)
3. 1 OR 2
4. TS=(hepatectomy)
5. TS=(liver neoplasms)
6. 3 AND 4 AND 5
7. TI=(resection)
8. TI=(surgery)
9. TI=(hepatectomy)
10. 7 OR 8 OR 9
11. TI=(ablation)

12. TI=(injection)
13. TI=(embolization)
14. 11 OR 12 OR 13
15. TI=(liver)
16. TI=(hepato*)
17. 15 OR 16
18. TI=(neoplas*)
19. TI=(cancer)
20. TI=(tumor)
21. TI=(tumour)
22. TI=(carcinoma)
23. TI=(oncolog*)
24. 18 OR 19 OR 20 OR 21 OR 22 OR 23
25. 10 AND 14 AND 17 AND 24
26. 3 AND 5
27. TI=(TACE)
28. TI=("transarterial chemoembolization")
29. 27 OR 28
30. TI=(RFA)
31. TI=("radiofrequency ablation")
32. TI=("RF ablation")
33. TI=("radiofrequency thermal ablation")
34. TI=(RTA)
35. 30 OR 31 OR 32 OR 33 OR 34
36. TI=(PEI)
37. TI=("ethanol injection")
38. TI=("ethanol ablation")
39. TI=("alcohol ablation")
40. 36 OR 37 OR 38 OR 39
41. TI=("microwave ablation")
42. TI=("microwave thermal ablation")

43. TI=(MWA)
44. 41 OR 42 OR 43
45. 29 OR 35 OR 40 OR 44
46. 46 AND 17 AND 24
47. 6 OR 25 OR 26 OR 46

Table S1.
Summary of the studies included in the network meta-analysis.

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2002 [19]	Prospective cohort	China	HCC	0.3-2	RFA	15(15)	13/2	61.8 (38-78)	4.1 (2.4-6.0)	NA	0.80(1y)	0.80(1y)	NA
					TR	15(15)	12/3	57.8 (39-72)	4.6 (2.3-7.1)	NA	1.00(1y)	1.00 (1y)	NA
Lencioni 2003 [20]	RCT	Italy	HCC	1.9±0.8	RFA	52(69)	36/16	67±6 (52-78)	2.8±0.6	1.00(1y)	NA	1.00(1y)	15 pain and 10 fever
					PEI	50(73)	30/20	69±7.4 (40-82)	2.8±0.8	0.96(1y)	NA	0.96(1y)	13 pain and 5 fever
Lin 2004 [21]	RCT	China	HCC	2±0.9	RFA	52(69)	35/17	62±11	2.9±0.8	0.76(3y)	NA	0.35(3y)	1 transient pleural effusion
					PEI	52(67)	34/18	59±10	2.8±0.8	0.66(3y)	NA	0.17(3y)	1 pain
Vivarelli 2004 [22]	Retrospective cohort	Italy	HCC	2.4	RES	79(92)	57/22	65.2±8.2 (43-81)	≤3/3.1-5 (21/58)	0.81(3y)	0.59(3y)	0.65(3y)	NA
					RFA	79(112)	67/12	67.8±8.7 (41-88)	≤3/3.1-5 (22/57)	0.50(3y)	0.25(3y)	0.33(3y)	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Cho 2005 [23]	Retrospective cohort	Korea	HCC	0.1-3	RES	61	48/13	57	3.4±1.0	NA	0.77(3y)	0.77(3y)	2 bleeding, 1 intraabdominal abscess, 1 wound infection
					RFA	99	76/23	58	3.1±0.8	NA	0.80(3y)	0.80(3y)	1 chest wall metastasis, 1 cholecystitis, 1 iatrogenic burn, 1 ileus, 1 hepatic infarction
Huang 2005 [25]	RCT	China	HCC	1-4.9	RES	38(42)	27/11	59±11.4	≤2/2.1-3 (24/14)	0.82	NA	0.82	NA
					PEI	38(46)	19/19	63±10.9	≤2/2.1-3 (21/17)	0.45	NA	0.45	NA
Hong 2005 [24]	Retrospective cohort	Korea	HCC	2.9(0.4-4.6)	RES	93	69/24	49.2±9.9	2.5±0.8	0.84(3y)	NA	0.84(3y)	NA
					RFA	55	41/14	59.1±9.6	2.4±0.6	0.73(3y)	NA	0.73(3y)	NA
Lin 2005 [26]	RCT	China	HCC	2.3±1	RFA	62(78)	40/22	61±10	2.5±1	0.74(3y)	NA	0.74(3y)	2 haemothorax, 1 gastric bleeding and perforation
					PEI	62(76)	39/23	60±8	2.3±0.8	0.60(3y)	NA	0.60(3y)	1 pain
Lu 2005 [27]	Retrospective cohort	China	HCC	2.1±1.1	RFA	53(72)	43/10	54.5±11.7 (24-74)	2.6±1.2 (1.0-6.1)	0.38(3y)	NA	0.38(3y)	2 skin burn, 1 puncture wound infection
					MWA	49(98)	44/5	50.1±13.7 (24-74)	2.5±1.2 (0.9-7.2)	0.51(3y)	NA	0.51(3y)	2 puncture wounds, 2 subcapsular hematoma
Montorsi 2005 [28]	Prospective cohort	Italy	HCC	2.1	RES	40	33/7	67±9	<5cm	NA	NA	0.73(3y)	NA
					RFA	58	43/15	67±6		NA	NA	0.60(3y)	NA
Shiina 2005 [29]	RCT	Japan	HCC	3.1(0.6-4.3)	RFA	118(184)	79/39	≤65/>65 (44/74)	≤2/>2 (45/73)	NA	NA	0.61(3y)	1 transient jaundice, 1 skin burn, 1 hepatic infarction, 3 neoplastic seeding

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					PEI	114(188)	87/27	≤65/>65 (41/73)	≤2/>2 (57/57)	NA	NA	0.45(3y)	1 abscess2 neoplastic seeding
Chen 2006 [30]	RCT	China	HCC	2.4±1	RES	90	75/15	49.4±10.9	≤3/3.1-5 (42/48)	0.53	NA	0.53	2 liver failure, 2 gastrointestinal bleeding, 27 ascites
					RFA	71	56/15	51.9±11.2	≤3/3.1-5 (37/34)	0.58	NA	0.58	3 skin burn
Lu 2006 [31]	RCT	China	Early HCC	1.8	RES	54(56)	37/17	49±14	3.2±1.0	NA	NA	0.86 (3y)	3 wound infection, 1 gastrointestinal bleeding
					RFA	51(57)	42/9	55±13	2.7±1.0	NA	NA	0.87 (3y)	1 peritoneal bleeding, 1 neoplastic seeding
Cho 2007 [32]	Retrospective cohort	Korea	HCC	5.7	RES	130(145)	103/27	56.3±8.8	≤2/2.1-3 (43/87)	0.66	NA	0.66	NA
					PEI	249(275)	181/68	57.7±9.7	≤2/2.1-3 (169/80)	0.49	NA	0.49	NA
Gao 2007 [33]	Retrospective cohort	China	HCC	4.6	RES	34(37)	28/6	51.5 (38-67)	2.58±0.41	0.76	NA	0.76	12 fever, 5 ascites
					RFA	53(84)	41/12	57.1 (31-81)	2.45±0.37	0.62	NA	0.62	2 bleeding, 1 fistula, 1 wound infection, 6 fever, 9 ascites
Lupo 2007 [34]	Retrospective cohort	Italy	HCC	2.6	RES	42	33/9	67(28-80)	4.0(3-5)	NA	0.43	0.43	2 urine infection, 1 bilioma, 1 pleural effusion, 1 renal failure, 1 intra-abdominal bleeding
					RFA	60	47/13	68(42-85)	3.65(3-5)	NA	0.32	0.32	2 liver failure, 1 hepatic abscess, 2 pleural effusion, 1 cutaneous metastasis
Zhou 2007 [35]	Retrospective cohort	China	HCC	0.5-5.9	RES	40(42)	35/5	53±13	≤2/2.1-5 (7/33)	NA	NA	0.75	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					RFA	47(54)	37/10	57±14	≤2/2.1-5 (8/39)	NA	NA	0.19	NA
Abu-Hilal 2008 [36]	Retrospective cohort	Italy and China	Early HCC	3.6	RES	34	26/8	67	3.8(1.3-5)	NA	0.56	0.56	3 hepatic failure
					RFA	34	27/7	65	3(2-5)	NA	0.56	0.56	1 artero-portal fistula
Brunello 2008 [37]	RCT	Italy	Early HCC	2.2	RFA	70(89)	49/20	70.3±8.1	1.27±0.54	0.60(3y)	NA	0.60(3y)	1 haemoperitoneum 1 right haemothorax
					PEI	69(88)	43/27	69.0±7.7	1.27±0.57	0.58(3y)	NA	0.58(3y)	1 haemoperitoneum 1 death
Guglielmi 2008 [38]	Retrospective cohort	Italy	HCC	2.3	RES	91(113)	73/18	≤65/>65 (47/44)	≤3/3.1-6 (31/60)	0.55	0.43	0.48	33 postoperative complications
					RFA	109(153)	88/21	≤65/>65 (38/71)	≤3/3.1-6 (32/77)	0.28	0.14	0.20	11 postoperative complications
Hiraoka 2008 [39]	Retrospective cohort	Japan	HCC	2.5	RES	59	44/15	62.4±10.6	2.27±0.55	0.59	NA	0.59	1 death, 2 abscess
					RFA	105	76/29	69.4±9.1	1.98±0.52	0.59	NA	0.59	1 biloma, 2 dermatitis
Bu 2009 [45]	Retrospective cohort	China	HCC	2.9(0.5-6)	RES	42(46)	36/6	53.93±10.74	≤3/3.1-5 (14/28)	0.57	0.46	0.50	1 postoperative hemorrhage, 3 pleural effusions, 2 subdiaphragmatic effusion
					RFA	46(54)	40/6	55.89±7.37	≤3/3.1-5 (20/26)	0.50	0.31	0.37	4 pleural effusions, 1 postoperative hemorrhage, 1 skin burn

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Ohmoto 2009 [40]	Retrospective cohort	Japan	HCC	2.8±2	RFA	34(37)	25/9	67 (44-78)	1.6 (0.7-2.0)	0.71	NA	0.71	2 pain, 4 fever, 1 bile duct injury, 1 pleural effusion, 1 skin burns, 1 vagovagal reflex
					MWA	49(56)	41/8	64 (38-75)	1.7 (0.8-2.0)	0.37	NA	0.37	11 pain, 17 fever, 9 bile duct injury, 8 pleural effusion, 5 ascites, 4 skin burns, 2 vagovagal reflex, 2 abscess, 2 intraperitoneal bleeding, 1 hepatic infarction, 1 portal thrombus, 1 biliary peritonitis
Sakaguchi 2009 [41]	Retrospective cohort	Japan	HCC	0.1-5	Laparoscopic /thoracoscopic RFA	249	169/80	65.6±8.9	2.48±0.89	0.57	NA	0.57	1 frequent premature ventricular contractions, 1 liver decompensation
					Laparoscopic /thoracoscopic MWA	142	107/35	64.9±7.8	2.28±0.74	0.63	NA	0.63	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Santambrogio 2009 [42]	Prospective cohort	Italy	HCC	3.2	RES	78	55/23	68±8	2.87±1.21	0.54	NA	0.54	15 extra-hepatic complications
					Laparoscopic RFA	74	59/15	68±7	2.63±1.07	0.41	NA	0.41	14 extra-hepatic complications
Shibata 2009 [43]	RCT	Japan	HCC	2.5±1.2	RFA	43(44)	33/10	69.8±8 (44-87)	1.6±0.5 (0.8-2.6)	0.84(3y)	NA	0.84(3y)	1 pseudoaneurysm

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					TR	46(49)	31/15	67.2±8.9 (45-83)	1.7±0.6 (0.9-3.0)	0.85(3y)	NA	0.85(3y)	1 hepatic infarction
Ueno 2009 [44]	Retrospective cohort	Japan	HCC	3(0.3-7.9)	RES	123(136)	82/41	67(28-85)	2.7±0.1	0.81	0.72	0.80	NA
					RFA	155(209)	100/55	66(40-79)	2.0±0.1	0.38	0.78	0.63	NA
Guo 2010 [46]	Retrospective cohort	China	HCC	2.5	RES	73(155)	57/16	50.0 (17.0-68.0)	≤3/3.1-5 (30/43)	0.27	0.47	0.44	1 postoperative hemorrhage, 5 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	86(211)	63/23	52.5 (26.0-80.0)	≤3/3.1-5 (42/44)	0.33	0.16	0.21	1 postoperative hemorrhage, 1 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Huang 2010 [47]	RCT	China	HCC	3.87	RES	115(144)	85/30	55.91±12.68	≤3/3.1-5 (45/44)	0.82	0.73	0.76	1 hepatic failure, 13 ascites, 5 effusion, 9 bile leakage, 2 postoperative bleeding, 2 gastrointestinal bleeding
					RFA	115(147)	79/36	56.57±14.30	≤3/3.1-5 (57/27)	0.61	0.52	0.55	1 gastric perforation, 2 hemorrhage, 1 malignant seeding, 1 hepatic infarction
Kagawa 2010 [48]	Retrospective cohort	Japan	Early HCC	4.2	RES	55(69)	40/15	66.1±8.4	≤2/2.1-5 (9/46)	0.42	NA	0.42	2 deaths, 1 liver failure, 1 pleural effusion, 1 pneumonia, 2 biliary leakage
					TR	62(79)	39/23	67.5±8.4	≤2/2.1-5 (19/43)	0.29	NA	0.29	1 duodenal perforation, 1 hemothorax
Morimoto	RCT	Japan	HCC	2.7	RFA	18(25)	12/6	73 (48-84)	3.7±0.6	NA	0.78(3y)	0.78(3y)	5 pain, 2 pleural effusion

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
2010 [49]					TR	19(21)	15/4	70 (57-78)	3.6 ±0.7	NA	0.95(3y)	0.95(3y)	1 pain, 1 pleural effusion
Azab 2011 [50]	RCT	Egypt	HCC	1.5	RFA	30(33)	75/15	46-77	<5cm	NA	NA	0.90	5 superficial burn, 17 transient pain, 3 portal vein thrombosis, 7 fever, 1 ascites
					PEI	30(32)				NA	NA	0.83	2 portal vein thrombosis, 3 fever, 3 ascites
Giorgio 2011 [51]	RCT	Italy	HCC	1.8	RFA	142	105/37	70 ±2 (68-74)	2.34 ±0.45 (1.1-3)	0.70	NA	0.70	1 major complication
					PEI	143	102/41	72 ±6 (68-79)	2.27 ±0.48 (1.3-2.9)	0.68	NA	0.68	3 major complication
Hung 2011 [52]	Retrospective cohort	China	Early HCC	3.5 ±2	RES	229	184/45	60.07 ±12.56	2.88 ±1.06	0.77	NA	0.77	NA
					RFA	190	121/69	67.42 ±11.45	2.37 ±0.92	0.67	NA	0.67	NA
Nishikawa 2011 [53]	Retrospective cohort	Japan	HCC	3.3	RES	69	50/19	67.4 ±9.7	2.68 ±0.49	0.74	NA	0.74	2 bile leakage, 2 ascites, 1 acute respiratory distress syndrome, 1 gastrointestinal bleeding
					RFA	162	95/67	68.4 ±8.7	1.99 ±0.62	0.63	NA	0.63	1 biloma, 1 ascites, 1 intra-abdominal bleeding
Yun 2011 [54]	Retrospective cohort	Korea	HCC	3.5(0.1-9.1)	RES	215	171/44	51.7 ±9.7	2.1 ±0.5	0.94	NA	0.94	NA
					RFA	255	197/58	57.0 ±9.9	2.1 ±0.5	0.87	NA	0.87	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2011 [55]	Retrospective cohort	China	HCC	0.5-3.5	RES	103(117)	78/25	56.4±15.2	<5cm	NA	NA	0.35(3y)	12 wound infection, 5 postoperative hemorrhage, 2 hepatic failure, 15 pleural effusions, 6 pleural effusions
					RFA	85(106)	62/23	58.5±12.9	<5cm	NA	NA	0.39(3y)	2 gallbladder cardiac reflex, 4 postoperative hemorrhage, 3 pleural effusions
Feng 2012 [57]	RCT	China	HCC	3	RES	84(116)	75/9	47 (18-76)	2.6±0.8	0.62(3y)	NA	0.62(3y)	7 pleural effusion, 3 pneumonia, 1 effusion plus infection, 3 wound infection or dehiscence, 1 biliary fistula, 2 abdominal bleeding, 1 pneumothorax or hemothorax
					RFA	84(120)	79/5	51 (24-83)	2.4±0.6	0.55(3y)	NA	0.55(3y)	5 pleural effusion, 1 liver abscess, 2 abdominal bleeding
Peng 2012 [58]	Retrospective cohort	China	Recurrent HCC	4.9	RES	74	65/9	51.5±12.1 (24-75)	1.1±0.5 (0.8-2.0)	0.62	NA	0.62	1 liver failure, 2 gastrointestinal bleeding, 1 peritoneal bleeding, 1 intestinal obstruction, 1 spontaneous bacterial peritonitis, 1 persistent jaundice, 31 ascites
					RFA	71	63/8	53.1±12.1 (28-74)	1.2±0.6 (0.9-2.0)	0.72	NA	0.72	1 gastrointestinal bleeding, 1 persistent jaundice, 12 ascites

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Peng 2012 [59]	RCT	China	Recurrent HCC	3.3±1.8	RFA	70(76)	55/15	55.1±9.5 (22-75)	≤3/3.1-5 (46/24)	NA	0.17	0.36	1 persistent jaundice, 1 ascites, 22 fever, 45 pain, 4 vomiting
					TR	69(74)	59/9	57.5±10.0 (19-75)	≤3/3.1-5 (41/28)	NA	0.39	0.46	1 liver failure, 1 ascites, 27 fever, 50 pain, 42 vomiting
Signoriello 2012 [60]	Retrospective cohort	Italy	HCC	0.1-9	RES	34(44)	30/4	62±7	≤3/3.1-5/>5.1 (13/9/4)	NA	NA	0.29	NA
					RFA	50(74)	40/10	68±7	≤3/3.1-5/>5.1 (24/11/7)	NA	NA	0.15	NA
					PEI	256(349)	188/68	67±8	≤3/3.1-5/>5.1 (143/43/12)	NA	NA	0.20	NA
a. Wang 2012 [61]	Retrospective cohort	China	Early HCC	2.5	RES	52	38/14	≤60 (35)	NA	NA	NA	0.92	NA
					RFA	91	60/31	≤60 (40)		NA	NA	0.73	NA
b. Wang 2012 [62]	Retrospective cohort	China	Early HCC	2.5	RES	208	168/40	≤60 (113)	≤2/2.1-5 (6/202)	NA	NA	0.77	NA
					RFA	254	161/93	≤60 (85)	≤2/2.1-5 (60/194)	NA	NA	0.57	NA
Desiderio 2013 [62]	Retrospective cohort	Italy	HCC	4.3(2.3-5)	RES	52(94)	37/15	65.6±4.8	≤3	0.46	NA	0.46	2 hepatic failure, 1 biliary fistula, 2 hemoperitoneum, 9 ascites
					RFA	44(81)	35/9	64.4±6.5		0.36	NA	0.36	6 pain, 7 fever
Ding 2013 [63]	Retrospective cohort	China	HCC	2.3±1.3	RFA	85(98)	68/17	58.64±8.52 (40-77)	2.38±0.81 (1.0-4.8)	0.82(3y)	NA	0.82(3y)	1 frequent premature ventricular contractions, 1 liver decompensation

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					MWA	113(131)	85/28	59.06 ±11.68 (30-86)	2.55 ±0.89 (0.8-5.0)	0.78(3y)	NA	0.78(3y)	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Guo 2013 [64]	Retrospective cohort	China	HCC	2.7	RES	102(129)	94/8	51.5(18-75)	≤3/3.1-5 (75/27)	NA	NA	0.63	5 postoperative hemorrhage, 3 bile leak, 4 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	94(125)	78/16	56(19-75)	≤3/3.1-5 (62/32)	NA	NA	0.50	1 postoperative hemorrhage, 2 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Hasegawa 2013 [65]	Retrospective cohort	Japan	HCC	2.2	RES	5361(6461)	3967/1394	66 (48-77)	2.3 (1.2-3)	0.71	NA	0.71	NA
					RFA	5548(7412)	3569/1979	69 (52-80)	2 (1-3)	0.61	NA	0.61	NA
					PEI	2059(2836)	1303/756	69 (52-80)	1.7 (1-3)	0.56	NA	0.56	NA
Iida 2013 [66]	Retrospective cohort	Japan	HCC	0.1-7.5	Laparoscopic RFA	18(27)	NA	73.5 ±4.0	2.1 ±0.5	0.78	NA	0.78	1 abscess
					Laparoscopic MWA	40(56)		70.1 ±6.6	2.0 ±0.9	0.78	NA	0.78	1 abscess
Imai 2013 [67]	Retrospective cohort	Japan	HCC	4.1	RES	101	75/26	63.3 ±9.7	2.14 ±0.55	0.87	NA	0.87	NA
					RFA	82	46/36	67.6 ±8.5	1.87 ±0.50	0.60	NA	0.60	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Kim 2013 [68]	Retrospective cohort	Korea	Early HCC	0.1-4.2	RES	47	36/11	58.8 ±10.7	3.66 ±0.76	NA	0.85(3y)	0.85(3y)	2 pleural effusion, 2 pneumonia, 1 hepatic failure, 1 hepatic abscess, 1 mechanical ileus
					TR	37	31/6	61.7 ±11.1	3.46 ±0.75	NA	0.78(3y)	0.78(3y)	1 bile duct dilatation
Lai 2013 [69]	Retrospective cohort	China	HCC	2.9 ±1.5	RES	80	55/25	60.8 ±9.9	2.9 ±1.1	0.71	NA	0.71	NA
					RFA	31	19/12	63.1 ±12.8	1.8 ±0.6	0.84	NA	0.84	NA
Lin 2013 [70]	Retrospective cohort	China	Early HCC	3.4	RFA	658	393/265	64.7 ±10.5	2.4 ±1.1 (0.8-9.5)	0.60	0.50	0.55	NA
					PEI	378	243/135	63.5 ±12.1	2.0 ±0.9 (0.4-7.0)	0.50	0.28	0.40	NA
Peng 2013 [71]	RCT	China	HCC	0.6-5.2	RFA	95(133)	71/24	55.3 ±13.3	3.39 ±1.35	NA	0.59(3y)	0.59(3y)	51 pain, 26 fever, 29 vomiting, 4 ascites, 2 pleural effusion, 1 skin burn, 1 abdominal infection, 1 small intestinal obstruction
					TR	94(137)	75/19	53.3 ±11	3.47 ±1.44	NA	0.67(3y)	0.67(3y)	57 pain, 33 fever, 40 vomiting, 5 ascites, 3 pleural effusion, 1 skin burn, 1 bile duct stenosis, 1 gastric hemorrhage
Tohme 2013 [72]	Retrospective cohort	America	Early HCC	2.4	RES	50(62)	31/19	66.3 ±1	3.07 ±1.17	0.48	NA	0.48	3 pleural effusion, 1 pneumonia, 1 myocardial infarction, 2 biloma, 2 ileus, 1 ascites, 1 hyperbilirubinaemia >6, 1 renal insufficiency, 2 encephalopathy

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					RFA	60(75)	38/22	65.6±12	2.36±0.94	0.35	NA	0.35	1 oesophagitis, 3 encephalopathy, 1 cholangitis, 2 ascites, 1 renal insufficiency, 1 pneumonia
Wong 2013 [73]	Retrospective cohort	China	Early HCC	0.1-5	RES	46	30/16	55.1±12	2.1±0.6	0.85	NA	0.85	2 fever, 1 increased serum alanine aminotransferase level, 2 atelectasis, 2 biloma
					RFA	36	18/18	63.5±13	1.9±0.6	0.72	NA	0.72	None
Zhang 2013 [74]	Retrospective cohort	China	HCC	2.2±1	RFA	78(97)	64/14	54±10.5 (30-80)	≤3/3.1-5 (47/31)	0.43	0.39	0.41	1 persistent jaundice, 1 biliary fistula
					MWA	77(105)	67/10	54±9.5 (26-76)	≤3/3.1-5 (36/41)	0.58	0.29	0.39	1 hemothorax and intrahepatic hematoma, 1 peritoneal hemorrhage
Abdelaziz 2014 [75]	RCT	Egypt	Early HCC	2.3	RFA	45(52)	31/14	56.8±7.3	2.95±1.03	0.68(1y)	NA	0.68(1y)	2 subcapsular hematoma, 1 thigh burn, 2 pleural effusion
					MWA	66(76)	48/18	53.6±5	2.9±0.97	0.96(1y)	NA	0.96(1y)	1 subcapsular hematoma, 1 abdominal wall skin burn
Shi 2014 [76]	Retrospective cohort	China	HCC	3.8	RES	107(126)	87/20	54.5±9.9	≤3/3.1-5 (37/54)	0.73	0.57	0.60	NA
					MWA	117(143)	93/24	56.6±9.2	≤3/3.1-5 (40/56)	0.65	0.52	0.52	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Yang 2014 [77]	Retrospective cohort	Korea	HCC	0.1-7	RES	52	38/14	55.7 ±10.6	≤2/2.1-5 (21/31)	0.94	NA	0.94	2 pneumonia, 1 wound infection, 1 biliary anastomotic leak, 1 portal vein thrombosis, 1 nausea, 1 delirium, 4 ascites
					RFA	79	59/20	57.2 ±9.2	≤2/2.1-5 (36/43)	0.86	NA	0.86	1 vomiting, 1 ascites, 6 abdominal pain, 2 nausea, 1 sinus bradycardia
Zhang 2014 [78]	Retrospective cohort	China	Recurrent HCC	2.7	RES	27(29)	25/2	47 ±13	3.2 ±1.0	NA	NA	0.63	NA
					MWA	39(46)	37/2	52 ±13	2.7 ±1.1	NA	NA	0.62	NA
Pompili 2015 [79]	Retrospective cohort	Italy	Early HCC	2.8	RFA	136	75/61	68 (41-85)	1.8 (1-2)	0.63	NA	0.63	2 ascites, 1 pleural effusion, 1 hemobilia
					PEI	108	90/18	68.5 (34-86)	1.95 (0.8-2)	0.65	NA	0.65	1 hemobilia, 1 portal vein thrombosis
Xu 2015 [80]	RCT	China	HCC	0.1-3	Laparoscopic RES	45	34/11	58.3 ±3.1 (26-78)	3.6 ±0.7 (1-5)	NA	0.38(3y)	0.38(3y)	3 bile leakage, 3 pleural effusion, 2 postoperative hemorrhage
					MWA	45	32/13	57.9 ±3.4 (27-76)	3.8 ±0.9 (2-5)	NA	0.33(3y)	0.33(3y)	1 bile leakage, 1 pleural effusion, 1 postoperative hemorrhage

HCC: hepatocellular carcinoma;

BCLC: Barcelona Clinic Liver Cancer;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

RCT: randomized controlled trial;

NA: not available.

Table S2.

Quality assessment of included studies using GRADE framework.

Intervention/Comparator	Illustrative comparative risks* (per 1000, 95% CI)		Relative effect of survival time (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Comparator Assumed survival risk	Corresponding survival risk with intervention			
1-year OS rate					
RES/MWA	923	984 (932 to 997)	**OR 5.25 (1.15 to 23.97)**	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	947	944 (902 to 968)	OR 0.94 (0.52 to 1.71)	990 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	835	802 (674 to 889)	OR 0.80 (0.41 to 1.58)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	944	963 (906 to 1000)	OR 1.02 (0.96 to 1.09)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	932	945 (931 to 956)	OR 1.25 (0.99 to 1.60)	5006 (30 studies)	⊕⊕⊕⊕ high

RES/TR	939	904 (765 to 965)	OR 0.61 (0.21 to 1.79)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	938	802 (310 to 978)	OR 0.27 (0.03 to 2.90)	31 (1 study)	⊕⊕⊖⊖ low
3-year OS rate					
RES/MWA	712	734 (623 to 822)	OR 1.12 (0.67 to 1.87)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	736	779 (717 to 828)	OR 1.26 (0.91 to 1.73)	987 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	499	536 (421 to 645)	OR 1.16 (0.73 to 1.83)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	729	748 (657 to 822)	OR 1.10 (0.71 to 1.71)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	785	851 (823 to 875)	**OR 1.57 (1.28 to 1.93)**	15906 (30 studies)	⊕⊕⊕⊖ moderate
RES/TR	798	760 (618 to 860)	OR 0.80 (0.41 to 1.55)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	737	611 (516 to 704)	OR 0.56 (0.38 to 0.85)	454 (4 studies)	⊕⊕⊕⊖ moderate
5-year OS rate					
RES/MWA	545	607 (492 to 712)	OR 1.29 (0.81 to 2.07)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	545	609 (442 to 756)	OR 1.30 (0.66 to 2.58)	687 (4 studies)	⊕⊕⊖⊖ low

RES/PEI	293	436 (334 to 545)	**OR 1.87 (1.21 to 2.90)**	519 (3 studies)	⊕⊕⊕⊖ moderate
RFA/PEI	533	496 (368 to 624)	OR 0.86 (0.51 to 1.45)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	601	744 (705 to 779)	**OR 1.93 (1.59 to 2.34)**	15154 (25 studies)	⊕⊕⊕⊖ moderate
RES/TR	290	419 (251 to 607)	OR 1.76 (0.82 to 3.78)	117 (1 study)	⊕⊕⊖⊖ low
RFA/TR	464	356 (222 to 523)	OR 0.64 (0.33 to 1.27)	139 (1 study)	⊕⊕⊕⊖ moderate

The absolute and relative risk of survival with treatments*. GRADE: Grading of Recommendations, Assessment, Development and Evaluation. *The results presented in the Table S1 were built around the assumption of a consistent relative effect. The implications of this effect for populations were considered at different baseline risks. Based on the assumed risks, corresponding risks after an intervention were calculated using the meta-analytic risk ratio.

Table S3.
Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in RCT.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	12			10			4		
RES		2	3.06		1	1.80		1	1.25
RFA		3	3.21		3	2.56		2	2.08
MWA		1	1.14		NA	NA		NA	NA
TR		4	3.22		2	2.38		NA	NA
PEI		5	4.36		4	3.26		3	2.68

3-5cm	4			4			2		
RES		1	1.17		1	1.19		1	1.69
RFA		3	2.88		3	2.91		3	2.60
MWA		NA	NA		NA	NA		NA	NA
TR		2	1.94		2	1.90		2	1.71
PEI		NA	NA		NA	NA		NA	NA
All tumours (≤ 5cm)	18			14			5		
RES		3	2.78		2	2.43		1	1.68
RFA		4	3.91		3	3.52		3	2.75
MWA		1	1.62		4	3.10		NA	NA
TR		2	1.79		1	1.68		2	2.09
PEI		5	4.90		5	4.27		4	3.48

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S4.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in all studies.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	44			42			31		
RES		3	3.02		2	2.49		1	1.35
RFA		4	3.16		3	3.44		2	3.03
MWA		2	2.19		4	3.52		4	3.31
TR		1	2.05		1	1.66		3	3.18

PEI		5	4.58		5	3.89		5	4.13
3-5cm	17			16			11		
RES		1	1.23		1	1.10		1	1.93
RFA		4	3.52		3	3.43		3	3.18
MWA		3	3.46		4	3.72		4	3.43
TR		2	1.97		2	2.10		2	1.94
PEI		5	4.82		5	4.66		5	4.53
All tumours (⩽ 5cm)	62			57			40		
RES		2	2.34		2	2.18		1	1.32
RFA		3	3.27		3	3.48		3	3.36
MWA		4	3.78		4	3.98		4	3.51
TR		1	1.10		1	1.27		2	2.45
PEI		5	4.52		5	4.10		5	4.36

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S5.

Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	1.01 (0.40-2.14)	0.98 (0.77-1.26)
MWA vs RES	**161.8 (1.39-581.0)**	NA
TR vs RES	15.61 (0.02-54.78)	NA
PEI vs RES	0.68 (0.19-1.76)	1.03 (0.54-1.94)

MWA vs RFA	**154.8 (1.74-590.1)**	1.42 (0.63-3.19)
TR vs RFA	13.24 (0.02-55.15)	1.00 (0.56-1.80)
PEI vs RFA	0.68 (0.28-1.36)	0.97 (0.78-1.19)
TR vs MWA	1.42 (0-5.94)	NA
PEI vs MWA	**0.08 (0-0.42)**	NA
PEI vs TR	10.75 (0.01-29.11)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.86 (0.40-1.68)	0.92 (0.71-1.19)
MWA vs RES	NA	NA
TR vs RES	1.44 (0.14-5.50)	NA
PEI vs RES	0.75 (0.28-1.89)	1.21 (0.59-2.15)
MWA vs RFA	NA	NA
TR vs RFA	1.64 (0.20-5.84)	1.01 (0.55-1.87)
PEI vs RFA	0.88 (0.44-1.79)	0.91 (0.71-1.17)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.29 (0.13-4.99)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.71 (0.10-2.47)	0.93 (0.62-1.37)
MWA vs RES	NA	NA
TR vs RES	NA	NA
PEI vs RES	0.49 (0.04-2.02)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	NA	NA
PEI vs RFA	0.93 (0.08-3.85)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S6.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in

RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.25 (0-1.47)	0.89 (0.45-1.77)
MWA vs RES	NA	NA
TR vs RES	1.00 (0-5.0)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.40 (0.64-11.93)	1.10 (0.78-1.55)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.24 (0-1.25)	0.70 (0.34-1.45)
MWA vs RES	NA	NA
TR vs RES	1.14 (0-6.20)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.98 (0.71-15.22)	1.29 (0.87-1.89)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
5-year OS rate for treatment vs reference		
RFA vs RES	1.05 (0.03-5.33)	0.71 (0.32-1.57)
MWA vs RES	NA	NA
TR vs RES	12.87 (0.02-44.43)	NA
PEI vs RES	NA	NA

MWA vs RFA	NA	NA
TR vs RFA	7.64 (0.14-42.49)	1.93 (0.53-7.06)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S7.

Survival rates (1-year, 3-year and 5-year) for lesion (≤5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.65 (0.28-1.31)	0.96 (0.77-1.20)
MWA vs RES	2.75 (0.52-9.18)	0.98 (0.54-1.78)
TR vs RES	2.15 (0.49-6.46)	NA
PEI vs RES	**0.42 (0.14-0.98)**	1.03 (0.54-1.94)
MWA vs RFA	4.62 (0.85-15.59)	1.42 (0.63-3.19)
TR vs RFA	**3.3 (1.05-8.21)**	1.09 (0.84-1.43)
PEI vs RFA	0.65 (0.32-1.14)	0.95 (0.80-1.14)
TR vs MWA	1.26 (0.14-4.73)	NA
PEI vs MWA	**0.24 (0.03-0.81)**	NA
PEI vs TR	**0.26 (0.06-0.69)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.80 (0.36-1.69)	0.87 (0.69-1.10)
MWA vs RES	1.18 (0.16-4.30)	0.88 (0.39-1.98)
TR vs RES	1.69 (0.47-4.87)	NA
PEI vs RES	0.66 (0.23-1.78)	1.12 (0.59-2.15)
MWA vs RFA	1.71 (0.17-6.61)	NA
TR vs RFA	2.09 (0.81-4.65)	1.20 (0.90-1.60)

PEI vs RFA	0.83 (0.39-1.73)	0.84 (0.66-1.07)
TR vs MWA	3.25 (0.24-14.23)	NA
PEI vs MWA	1.25 (0.11-5.36)	NA
PEI vs TR	0.49 (0.13-1.33)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.11-2.48)	0.85 (0.61-1.17)
MWA vs RES	NA	NA
TR vs RES	2.96 (0.05-14.7)	NA
PEI vs RES	0.49 (0.04-2.03)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	3.59 (0.14-18.06)	1.30 (0.70-2.41)
PEI vs RFA	0.90 (0.08-3.65)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.51 (0.02-7.71)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S8.

Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		

RFA vs RES	1.03 (0.42-2.07)	1.00(0.95-1.05)
MWA vs RES	1.55 (0.41-4.10)	1.00(0.53-1.89)
TR vs RES	2.51 (0.26-9.65)	1.00(0.56-1.80)
PEI vs RES	0.71 (0.24-1.60)	1.00 (0.93-1.07)
MWA vs RFA	1.51 (0.60-3.11)	1.02 (0.85-1.23)
TR vs RFA	2.45 (0.33-8.72)	1.00(0.56-1.80)
PEI vs RFA	0.69 (0.39-1.13)	0.99 (0.93-1.06)
TR vs MWA	1.96 (0.21-7.87)	NA
PEI vs MWA	0.55 (0.18-1.29)	NA
PEI vs TR	0.56 (0.07-2.13)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.85 (0.40-1.62)	**0.94 (0.90-0.99)**
MWA vs RES	0.87 (0.31-1.96)	0.96 (0.49-1.87)
TR vs RES	1.87 (0.40-5.56)	1.17 (0.67-2.04)
PEI vs RES	0.80 (0.33-1.68)	1.00 (0.71-1.40)
MWA vs RFA	1.02 (0.54-1.76)	1.00 (0.82-1.22)
TR vs RFA	2.21 (0.60-5.76)	1.01 (0.55-1.87)
PEI vs RFA	0.95 (0.59-1.47)	0.97 (0.90-1.03)
TR vs MWA	2.35 (0.54-6.80)	NA
PEI vs MWA	1.01 (0.45-2.00)	NA
PEI vs TR	0.59 (0.15-1.67)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.58 (0.24-1.11)	**0.86 (0.81-0.90)**
MWA vs RES	0.58 (0.18-1.33)	0.89 (0.44-1.79)
TR vs RES	0.72 (0.11-2.48)	0.69 (0.34-1.42)
PEI vs RES	**0.46 (0.18-0.95)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.00 (0.50-1.77)	1.02 (0.78-1.33)
TR vs RFA	1.24 (0.25-3.80)	NA
PEI vs RFA	0.81 (0.48-1.28)	**0.92 (0.85-0.99)**
TR vs MWA	1.37 (0.23-4.59)	NA
PEI vs MWA	0.90 (0.38-1.83)	NA

PEI vs TR	1.06 (0.19-3.41)	NA

Table S9.
Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.19 (0-1.18)	0.96 (0.78-1.17)
MWA vs RES	0.24 (0-1.61)	NA
TR vs RES	0.56 (0-3.31)	1.02 (0.55-1.88)
PEI vs RES	**0.10 (0-0.63)**	NA
MWA vs RFA	1.25 (0.31-3.46)	0.98 (0.49-1.95)
TR vs RFA	**2.92 (1.14-6.65)**	1.11 (0.80-1.54)
PEI vs RFA	0.50 (0.17-1.13)	0.89 (0.66-1.20)
TR vs MWA	3.46 (0.57-11.35)	NA
PEI vs MWA	0.60 (0.09-1.94)	NA
PEI vs TR	**0.21 (0.04-0.56)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	**0.14 (0.01-0.68)**	**0.78 (0.62-0.98)**
MWA vs RES	**0.15 (0-0.77)**	1.02 (0.57-1.81)
TR vs RES	0.36 (0.01-1.73)	0.92 (0.48-1.75)
PEI vs RES	**0.09 (0-0.44)**	NA
MWA vs RFA	1.01 (0.25-2.72)	0.60 (0.26-1.36)
TR vs RFA	2.37 (0.90-5.53)	1.29 (0.87-1.89)
PEI vs RFA	0.57 (0.10-1.83)	0.71 (0.50-1.00)
TR vs MWA	3.48 (0.62-11.64)	NA
PEI vs MWA	0.90 (0.08-3.36)	NA
PEI vs TR	0.30 (0.03-1.06)	NA
5-year OS rate for treatment vs reference		

RFA vs RES	0.91 (0.05-4.18)	**0.62 (0.45-0.85)**
MWA vs RES	1.79 (0.03-5.39)	0.90 (0.48-1.69)
TR vs RES	14.49 (0.05-27.29)	NA
PEI vs RES	1.88 (0.01-3.18)	NA
MWA vs RFA	1.25 (0.18-3.84)	0.57 (0.21-1.51)
TR vs RFA	7.08 (0.25-26.41)	2.36 (0.66-8.37)
PEI vs RFA	0.79 (0.05-2.64)	**0.56 (0.37-0.84)**
TR vs MWA	13.88 (0.19-50.64)	NA
PEI vs MWA	1.88 (0.04-5.54)	NA
PEI vs TR	6.11 (0-3.02)	NA

Table S10.

Survival rates (1-year, 3-year and 5-year) for lesion (≤ 5cm) treatment comparisons estimated by direct, indirect and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.78 (0.37-1.49)	0.99 (0.95-1.04)
MWA vs RES	0.73 (0.28-1.55)	0.95 (0.71-1.27)
TR vs RES	2.35 (0.74-5.96)	1.04 (0.70-1.55)
PEI vs RES	0.61 (0.26-1.25)	1.01 (0.74-1.39)
MWA vs RFA	0.95 (0.48-1.67)	1.01 (0.85-1.21)
TR vs RFA	**3.01 (1.33-6.15)**	1.10 (0.85-1.43)
PEI vs RFA	0.78 (0.51-1.13)	0.98 (0.93-1.05)
TR vs MWA	**3.51 (1.78-8.52)**	0.91 (0.70-1.18)
PEI vs MWA	0.91 (0.41-1.79)	NA
PEI vs TR	**0.30 (0.11-0.63)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.78 (0.44-1.29)	**0.93 (0.89-0.98)**
MWA vs RES	0.72 (0.36-1.32)	0.96 (0.69-1.32)

TR vs RES	1.50 (0.64-3.08)	1.06 (0.69-1.61)
PEI vs RES	0.71 (0.37-1.30)	**0.93 (0.86-1.00)**
MWA vs RFA	0.94 (0.58-1.44)	0.95 (0.78-1.16)
TR vs RFA	**1.93 (1.05-3.29)**	1.20 (0.90-1.60)
PEI vs RFA	0.92 (0.63-1.32)	0.95 (0.89-1.01)
TR vs MWA	2.16 (0.99-4.16)	NA
PEI vs MWA	1.03 (0.56-1.77)	NA
PEI vs TR	**0.52 (0.25-0.96)**	NA
5-year OS rate for treatment vs reference		
RFA vs RES	**0.56 (0.27-0.99)**	**0.84 (0.80-0.89)**
MWA vs RES	0.56 (0.23-1.14)	0.90 (0.61-1.31)
TR vs RES	0.79 (0.24-1.92)	0.69 (0.34-1.42)
PEI vs RES	**0.47 (0.22-0.87)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.01 (0.60-1.59)	0.97 (0.75-1.25)
TR vs RFA	1.42 (0.58-2.96)	1.30 (0.70-2.41)
PEI vs RFA	0.85 (0.57-1.22)	**0.91 (0.84-0.98)**
TR vs MWA	1.50 (0.52-3.46)	NA
PEI vs MWA	0.90 (0.47-1.58)	NA
PEI vs TR	0.71 (0.26-1.57)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S11.

Posterior summaries from random effects consistency and inconsistency models for small lesion (<3cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.55	0.21	(0.15-1.00)	0.38	0.23	(0.02-0.88)
τ	11.06	88.80	(1.00-43.58)	4020	78840	(1.28-2366.00)
resdev	90.04	13.04	(66.16-117.10)	94.65	12.94	(70.06-120.70)
pD	59.96			57.5		
DIC	402.44			404.59		
3-year OS rate for treatment vs reference						
σ	0.59	0.14	(0.34-0.88)	0.6	0.14	(0.36-0.91)
τ	3.74	10.43	(1.29-8.74)	3.29	1.92	(1.21-8.05)
resdev	92.02	14.19	(66.64-122.10)	90.7	13.92	(65.64-120.00)
pD	70.71			71.74		
DIC	517.72			517.43		
5-year OS rate for treatment vs reference						
σ	0.53	0.12	(0.32-0.80)	0.55	0.13	(0.34-0.84)
τ	4.19	2.29	(1.57-9.74)	3.82	2.02	(1.42-8.83)
resdev	63.99	11.47	(43.52-88.24)	63.55	11.37	(43.39-87.90)
pD	54.24			54.99		
DIC	411.73			412.03		

Table S12.
Posterior summaries from random effects consistency and inconsistency models for lesion (3-5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.28	0.25	(0.01-0.92)	0.38	0.34	(0.02-1.28)
τ	42220	1.30E+06	(1.19-19650.00)	19500.00	720600.00	(0.62-4178.00)

resdev	28.90	6.96	(17.25-44.41)	32.18	7.36	(19.64-48.32)
pD	22.80			24.59		
DIC	152.25			157.31		
3-year OS rate for treatment vs reference						
σ	0.62	0.27	(0.17-1.24)	0.67	0.31	(0.14-1.40)
τ	9.02	65.04	(0.66-35.66)	49.29	1164.00	(0.51-48.58)
resdev	32.36	8.17	(18.39-50.07)	32.62	8.22	(18.52-50.51)
pD	28.02			28.65		
DIC	187.98			188.88		
5-year OS rate for treatment vs reference						
σ	0.80	0.46	(0.14-1.94)	0.60	0.42	(0.04-1.64)
τ	49.88	1159	(0.27-49.16)	5839.00	185600.00	(0.37-748.40)
resdev	22.54	6.73	(11.29-37.43)	22.57	6.519	(11.45-36.90)
pD	20.62			19.84		
DIC	132.23			131.49		

Table S13.

Posterior summaries from random effects consistency and inconsistency models for lesion (≤ 5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.49	0.13	(0.26-0.77)	0.29	0.14	(0.05-0.58)
τ	5.30	3.72	(1.70-14.33)	83.27	806.8	(2.94-391.70)
resdev	129.2	14.99	(101.40-160)	133.1	14.50	(105.70-162.80)
pD	84.95			78.28		
DIC	606.94			604.11		
3-year OS rate for treatment vs reference						
σ	0.50	0.09	(0.33-0.70)	0.47	0.096	(0.29-0.67)

τ	4.51	1.83	(2.08-9.02)	5.28	2.59	(2.24-11.80)
resdev	124	15.64	(95.16-156.40)	124.5	15.89	(95.35-157.50)
pD	93.89			93.37		
DIC	723.55			723.53		
5-year OS rate for treatment vs reference						
σ	0.44	0.10	(0.26-0.65)	0.44	0.1	(0.26-0.67)
τ	6.25	3.60	(2.38-14.90)	6.08	4.01	(2.25-14.87)
resdev	86.73	13.53	(62.35-115.40)	85.74	13.55	(61.39-114.40)
pD	67.86			68.84		
DIC	544.41			544.41		

sd: standard deviation;

CI: Credible Interval

σ: between-trial standard deviation

τ^2: between-trial variance

resdev: residual deviance

pD: effective number of parameters

DIC: deviance information criterion

Figure S1.

Results of the consistency test for closed loop at 1-year, 3-year, and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm.

i Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm

ii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm

iii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm

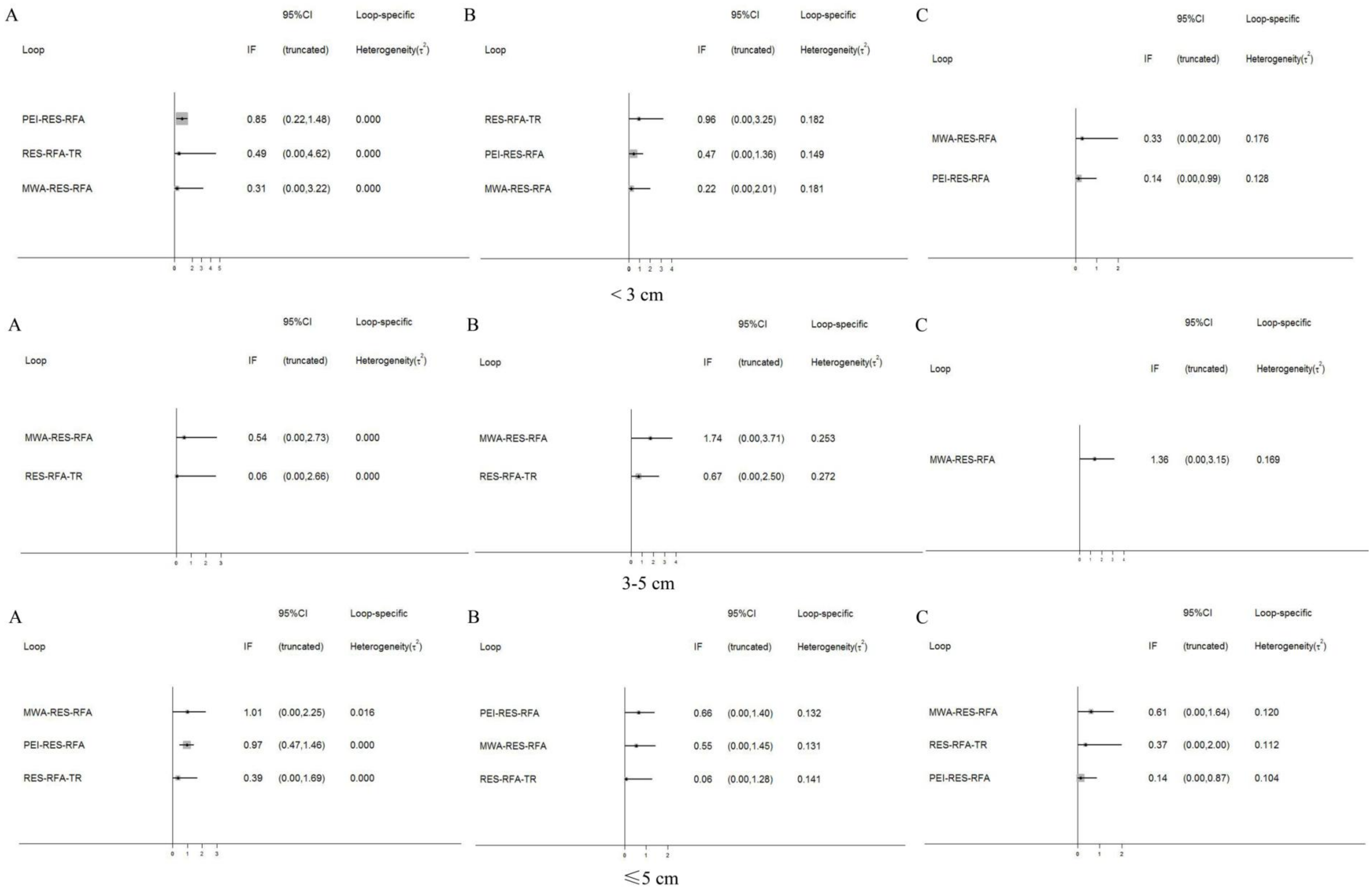

A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.85 (0.22,1.48) 0.000
RES-RFA-TR 0.49 (0.00,4.62) 0.000
MWA-RES-RFA 0.31 (0.00,3.22) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
RES-RFA-TR 0.96 (0.00,3.25) 0.182
PEI-RES-RFA 0.47 (0.00,1.36) 0.149
MWA-RES-RFA 0.22 (0.00,2.01) 0.181
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.33 (0.00,2.00) 0.176
PEI-RES-RFA 0.14 (0.00,0.99) 0.128
< 3 cm
A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.54 (0.00,2.73) 0.000
RES-RFA-TR 0.06 (0.00,2.66) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.74 (0.00,3.71) 0.253
RES-RFA-TR 0.67 (0.00,2.50) 0.272
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.36 (0.00,3.15) 0.169
3-5 cm
A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.01 (0.00,2.25) 0.016
PEI-RES-RFA 0.97 (0.47,1.46) 0.000
RES-RFA-TR 0.39 (0.00,1.69) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.66 (0.00,1.40) 0.132
MWA-RES-RFA 0.55 (0.00,1.45) 0.131
RES-RFA-TR 0.06 (0.00,1.28) 0.141
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.61 (0.00,1.64) 0.120
RES-RFA-TR 0.37 (0.00,2.00) 0.112
PEI-RES-RFA 0.14 (0.00,0.87) 0.104
≤5 cm

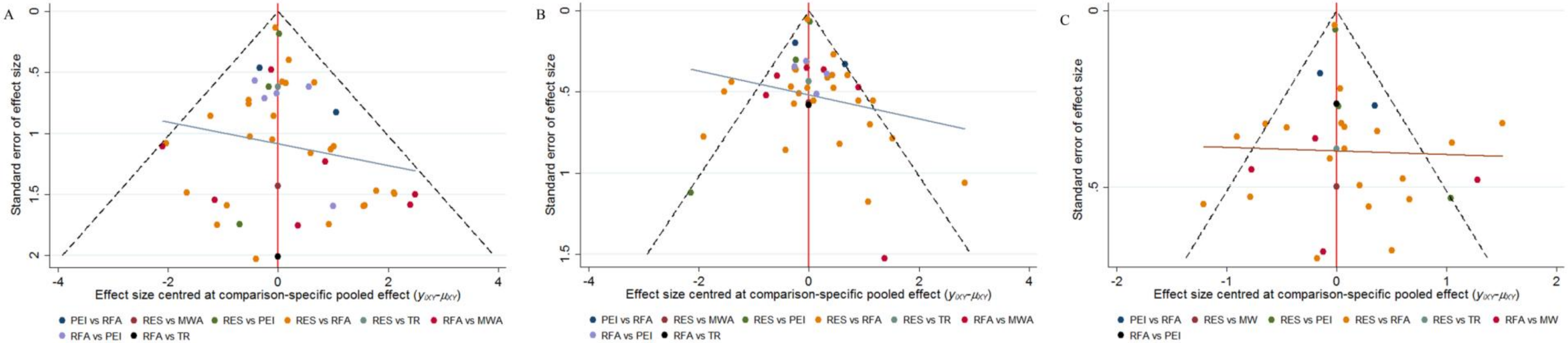
Figure S2.

Assessment of publication bias using funnel plot.

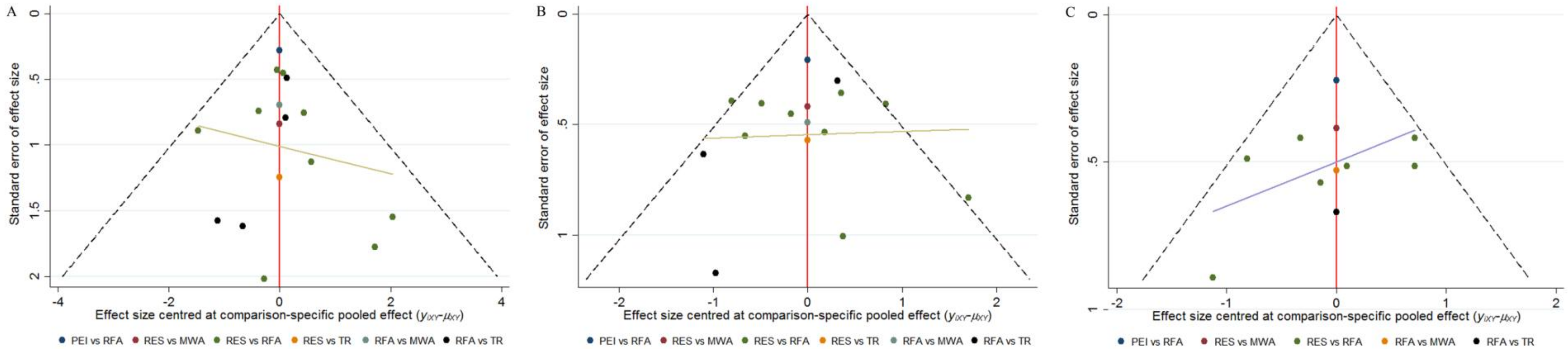
i Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm.

ii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm.

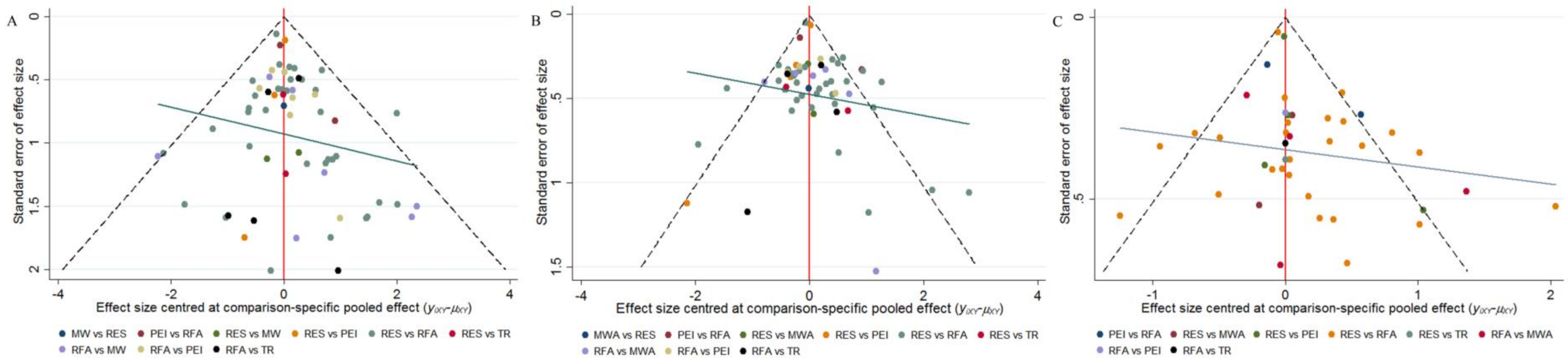
iii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm



i <3 cm



ii 3-5 cm



iii<5 cm

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8

METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).* _	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	11,12
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11,12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11,12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Palliative care, Radiology and imaging, Surgery
Keywords:	resection, radiofrequency ablation, microwave ablation, transcatheter arterial chemoembolization, percutaneous ethanol injection, hepatocellular carcinoma

Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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Number of figures and tables: 7 figures and 15 tables

List of abbreviations in order of appearance: HCC: hepatocellular carcinoma; RES: resection; RFA: radiofrequency ablation; MWA: microwave ablation; TACE: transcatheter arterial chemoembolization; PEI: percutaneous ethanol injection; GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TR: TACE plus RFA; OS: overall survival; MCMC: Markov Chain Monte Carlo; CrI: credible interval; SUCRA: surface under the cumulative ranking curve LPS: lipopolysaccharide; TNFα: tumor necrosis factor α; IL: interleukin; TGFβ: transforming growth factor β.

Conflict of interest: The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement: Because this is a meta-analysis, it is not available for Patient Consent. All data in this network meta-analysis have been provided in either the main manuscript or additional file.

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Author Contributions:

1. Conceived and designed the experiments: Hongcui Cao, Tian'an Jiang, Lanjuan Li

2. Performed the experiments: Guo Tian, Shigui Yang, Jinqiu Yuan, Diane Threapleton, Qiyu Zhao, Fen Chen, Tian'an Jiang

3. Analyzed the data: Guo Tian, Shigui Yang, Jinqiu Yuan, Qiyu Zhao

4. Contributed reagents/materials/analysis tools: Qiyu Zhao, Fen Chen

5. Wrote the manuscript: Guo Tian, Shigui Yang, Tian'an Jiang

6. Critically revised and approved the final version of manuscript: Diane Threapleton, Hongcui Cao, Tian'an Jiang, Lanjuan Li

7. Study supervision: Hongcui Cao, Tian'an Jiang, Lanjuan Li

Abstract

Objective: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

Methods and analyses: We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

Results: We identified 62 studies, including 23893 patients. After adjustment for study design, and in the full sample of studies, the treatments were ranked in order of good to bad as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI. The ranks were similar for 1 and 3-year survival, with RES and TR being the highest ranking treatments. In both smaller (<3cm) and larger tumors (3-5cm), RES and TR were also the two highest ranking treatments. There was little evidence of inconsistency between direct and indirect evidence.

Conclusion: The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival. However, many of the between-treatment comparisons were not statistically significant and, for now, selection of strategies for treatment will depend patient and disease characteristics. Additionally, much of the evidence was provided by non randomised studies and knowledge gaps still exist.

More head-to-head comparisons between both RES and TR, or other approaches, will be necessary to confirm these findings.

Key words: resection; radiofrequency ablation; microwave ablation; transcatheter arterial chemoembolization; percutaneous ethanol injection; hepatocellular carcinoma.

Strengths and limitations of this study:

1. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

2. We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

3. The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival.

4. A major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival.

5. All included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies.

Introduction

Cancer was the second leading cause of death in 2013, behind cardiovascular disease, and in 2013 more than 8 million people died from cancer globally [1-3]. Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and the 3rd leading cause of cancer death, with 5-year overall survival rates under 12% [4 5].

Hepatic resection (RES) is the traditional choice for patients with HCC, without cirrhosis and with good remaining liver function [6]. Despite nearly 70% 5-year survival, recurrence rates with surgery are high [7]. Repeated hepatectomies to lengthen survival are not often appropriate owing to multiple-site tumor recurrence or patient background of liver cirrhosis [8 9]. Many locoregional therapies have been developed including ablative treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), or microwave ablation (MWA), and trans-arterial therapies such as transcatheter arterial chemoembolization (TACE) or transarterial chemotherapy infusion (TACI). Locoregional therapies are minimally invasive and therefore are cheaper and faster to recover from, as compared to resection. Such approaches may be appropriate for patients with unresectable, small or multiple carcinomas or those with severe cirrhosis. However, there may be a greater risk of recurrence because of incomplete destruction of cancer cells at the treatment margin, as seen with RFA [10].

Selection of treatment strategy is determined by liver function, tumor stage and patient performance status [7], but much uncertainty still remains surrounding the comparative efficacy of different treatment approahces. A recent review of international guidelines for HCC found similarities but also some discrepancy in treatment allocation recommendations because of regional classification differences, secondary to a lack of solid or high-level evidence [11]. A recent review of therapies also revealed that there was no consensus on whether surgery or ablation was better for small tumors [7]. Some discrepancy in prevalence and treatment outcomes may remain in different regions because of local biology, available resources or expertise and access to care [11]. However, if we ever hope to achieve standardized and evidence-based therapy for HCC, the unanswered question surrounding relative treatment efficacy of RES compared to ablative locoregional therapies must be resolved.

Traditional meta-analysis is limited by existing head-to-head treatment comparisons within included studies. It is therefore not possible to gauge the relative benefit of two treatments that have never been directly compared in studies. Real-life treatment-decisions are hindered by gaps in existing evidence, but network meta-analysis enables integration of direct and indirect comparisons to provide estimates for relative comparisons across many treatments [12]. In order to investigate comparative effectiveness among RES and common locoregional ablative therapies, we performed a systematic review and network meta-analysis.

Search Strategy

We conducted a systematic review and report findings in accordance with PRISMA for Network Meta-Analyses (PRISMA-NMA) [13] (PRISMA NMA Checklist).

The following databases were searched: PubMed, Embase, Web of science and Scopus, up to December 2015, using these keywords: resection, surgery, hepatectomy, radiofrequency ablation, transarterial chemoembolization, microwave thermal ablation, ethanol injection, liver, cancer, tumor (Additional file 1: Text S1). No language restrictions were used. Bibliographies from other relevant review articles were cross-examined for potential missed studies. Disagreement was resolved by a third reviewer. Citations were downloaded into reference management software and duplicate citations were electronically or manually removed.

We systematically included the studies using the following criteria: 1) original data from prospective or retrospective cohort studies and randomized clinical trials (RCTs) in humans; 2) reporting at least two treatments, including resection or any local ablative therapy (RES, RFA, MWA, PEI, or TACE+RFA (TR)); 3) mean lesion size ≤ 5 cm; 4) evaluating overall survival rate not less than one year after first or recurrent treatments. Conference abstracts and case reports were excluded, as were older publications from studies with multiple publications.

Data Extraction and Study Quality

Two investigators independently extracted and cross-checked the data from the eligible studies: author, year, study design, country, disease type, inclusion criteria, treatment style, study size, gender, age, tumor size, follow-up duration, treatment complications and survival outcomes. If in disagreement, a third reviewer adjudicated. The level of evidence was appraised using the Grading of Recommendations

Assessment, Development and Evaluation (GRADE) guidance [14], which was classified into four levels of high, moderate, low, and very low. The quality score was downgraded according to 5 domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias while scores were upgraded according to large effect, appropriate control for plausible confounding, and dose-response gradient.

Data Analysis

Network meta-analysis was used if a ring or open evidence loop was available. When possible, pair-wise direct head-to-head comparisons were conducted to calculate the pooled odds ratio (OR) and its 95% confidence interval (CI). Between-study heterogeneity was evaluated using the tau-squared statistic (τ^2) [15]. A node-splitting analysis was applied to check the consistency between direct evidence (existing real reported comparisons) and indirect evidence (estimated treatment comparisons) for their agreement on a specific node [16]. Bayesian network meta-analysis with Markov Chain Monte Carlo (MCMC), through a consistency model, was utilized to estimate the pooled ORs and its 95% credible interval (CrI) for the direct and indirect comparisons [16]. The inconsistency model was used to check for heterogeneity due to chance imbalance in the distribution of effect modifiers. Consistency in every closed loop was checked by the loop-specific approach in order to estimate whether treatment survival effects were disturbed by variance in the distribution of potential confounding factors among the studies. In order to compare and rank survival rates of different treatments we examined all studies first and then separately assessed smaller (<3cm) and larger (3-5cm) tumors. Random-effect meta-regression models were used, with and without adjustment for study design (cohort or RCT) and subgroup analyses were also conducted for RCTs in order to examine treatment effectiveness. We appraised the ranking probabilities for all therapies for each intervention and the treatment hierarchy was ordered by the surface under the cumulative ranking curve (SUCRA) [17]. Sensitivity analysis was conducted to remove each study, in turn, and estimate the treatment effect in the remaining studies. Funnel plots were utilized to check the possible presence of publication bias or small-study bias [18]. In this study, we used Bayesian MCMC simulations by WinBUGS 1.4 and graphically presented the results using Stata 13.

Results

Study Characteristics

After screening, 62 relevant studies in 61 articles were identified, of which 18 were randomized controlled trials and 44 were cohort studies [19-80]. We excluded 61571 duplicate or non-relevant citations (Figure 1). The summary characteristics of these studies are shown in Additional file 1: Table S1. Overall, 23893 patients of mean age from 46 to 73.5 years, with approximately 29236 tumors, were assigned to receive RES, RFA, MWA, TR and PEI, and the mean follow-up ranged from 1.5 to 5.7 years. In addition, the numbers of connected studies to the lines (black) and sample size of each treatment (red) were shown in Figure 2 and 3, respectively.

Network Meta-Analysis Results

Ten possible treatment comparisons among the five interventions were examined in the included studies. Comparable survival estimates were made for each treatment (per 1000 patients) and the survival OR among each of the treatment comparisons, according to follow-up duration, are presented in Additional file 1: Table S2, along with estimation of the quality of evidence using GRADE criteria.

Across the range of treatment comparisons and follow-up durations, evidence was graded between low and high quality. Evidence was often graded as low quality owing to publication bias and graded as high quality owing to a larger number of participants in direct comparisons.

Survival probabilities (estimated using Meanrank) and ranks for the five treatments in patients with tumors <3cm, 3-5cm or ≤5cm (with and without adjustment for study design) are graphically displayed in Figures 2-5, and numerical details are given in Additional file 1: Table S3-S4. RES was consistently associated with greater survival (rank 1) compared to MWA, RFA, TR and PEI for the 5-year survival estimates. The ranks were similar for 1 and 3-year survival with RES or TR being ranked as 1 or 2 in most analyses. After adjustment for study design, and in the full sample of available studies (n=40), the treatments were ranked as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI (Table S4).

Efficacy comparisons from network meta-regression for all treatments are summarized in Table 1 and 2, according to follow-up duration and initial tumor size.

Compared to RES, the 5-year survival in all studies (trials and observational studies) for all tumors ≤5cm, was 0.47 (95%CrI 0.22 to 0.87) for PEI, 0.79 (95%CrI 0.24 to 1.92) for TR, 0.56 (95%CrI 0.23 to 1.14) for MWA and 0.56 (95%CrI 0.27 to 0.99) for RFA (Table 2). When examining the comparisons across all treatments, the only significant difference for tumors <3cm was for 5-year survival, and a significantly worse survival was observed for PEI compared to RES 0.46 (95%CrI 0.18 to 0.95). For tumors between 3 and 5 cm, no significant differences were observed at 5-year survival, but significantly worse 3-year survival was observed with PEI, MWA and RFA compared to RES (Table 2). Despite smaller number of studies in analyses of only RCTs, the pairwise comparisons showed similar results. However, all relative rankings should be interpreted with caution because most network meta-regression comparisons did not suggest a statistically significant difference between treatments. Detailed results of each comparison for survival rates are shown in Additional file 1: Table S5-S10**.**

Loop-specific methods detected no inconsistency between the pairwise and network meta-analysis for most closed loops in the network (Additional file 1: Figure S1). However, inconsistency was observed between direct and indirect comparisons for the following loops: lesions <3cm: RES-RFA-TR, PEI-RES-RFA, MWA-RES-RFA; lesions 3-5cm: MWA-RES-RFA, RES-RFA-TR; and lesions ≤5cm: RES-RFA-TR). In addition, tests for inconsistency were carried out (Additional file 1: Table S11-S13), which indicated a close relationship of between-trial heterogeneity and inconsistency between "direct" and "indirect" evidence.

Sensitivity Analysis and publication bias

No significant change was observed when any one study was deleted. Funnel plots indicated that the included studies in each group were distributed symmetrically around the vertical line (x=0), suggesting that no obvious evidence of publication bias or small-sample effect existed in this network (Additional file 1: Figure S2).

Discussion

There are many techniques for attaining a large ablated zone and complete necrosis of HCC and this comprehensive review addresses two of the more common treatments, namely resection and ablation. In this network meta-analysis, of the five examined therapies, the pooled data showed RES ranked best in full sample analysis with or without adjustment for study design. In both smaller (<3cm) and larger tumors (3-5cm) RES remained the highest ranking treatment. However, most of the individual treatment comparisons were not statistically significant and thus, RES may not be superior to all other therapies. Our evidence indicates locoregional therapies and particularily RES or TR (TACE+RFA) are associated with longer survival.

Our observation of better survival outcomes with TR may be through the advantage of dual mechanisms. With TR, TACE induces hypoxic injury on cancer cells through occlusion of blood vessels and is followed by local ablation. This combination therapy may result in a larger ablated zone [81], reduce the possibility of micrometastasis and recurrence, and thus, result in better survival outcomes than RFA alone.

While being more invasive, and despite risk of complications, RES was associated with better survival outcomes after 1 year, 3 years and 5 years. This may be due to removal of larger sections of liver than can be targeted with locoregional therapies, thus removing a larger area of potentially cancerous cells. Additionally, rat models indicate that the liver has the potential to quickly restore its original size after partial hepatectomy. This may be mediated via interactions of lipopolysaccharide (LPS), tumor necrosis factor (TNF)α, interleukin (IL)-6, and transforming growth factor β (TGFβ) [82]. However, evidence from rat models and human studies indicates that resection success is associated with resection size and regeneration is stunted with larger resections [83-85]. The safe limit for remnant liver volume in normal liver is approximately 30% of total liver volume, but this is estimated to rise to 40-50% in those with liver disease [83 86]. Liver resection is recognised as the mose efficient treatment for HCC but is only applicable for less than 30% of all patients (Morise 2014). However, developments in preoperative imaging tachniques, laproscopic surgery and newly developing combinations with chemotherapy may extend its application to more advanced tumors [86]. Furthermore, the consistent associations observed with all studies and only in RCTs indicates that patient selection bias in the observational studies does not wholly explain the better survival outcomes with RES.

Overall, we found PEI was associated with shorter survival than the other four therapies, a finding which is supported in previous studies [20 29]. One study reported RFA was superior to PEI in achieving short- and long-term survival outcomes, although PEI and RFA showed similar 5-year survival in lesions <3 cm [51]. The possible reason why PEI is less effective than RFA may be because lesions often have a thick capsule and therefore ethanol may not distribute through tissues.

There are several limitations in this study. Firstly, a major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival. Secondly, this study included both RCTs and observational studies, in which study designs and type of data collection may not be comparable. However, findings were consistent among both study designs. Thirdly, all included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies. Fourthly, for many individual comparisons, there were either no direct comparisons or comparisons from only a small number of studies. The lack of evidence may increase the risk of bias, which could enlarge or undervalue effect size, and may explain the small inconsistency seen between direct and estimated comparisons. Thus, we should be cautious in interpreting treatment rankings for the different survival times and for different size lesions. While adverse events from treatments may differ (not evaluated in detail in this review), by examining overall survival outcomes in our review, we have taken account of both long-term potential benefits and harms from treatments. The focus of these findings should therefore be on the overall observation that RES or TR may be superior in terms of survival, rather than focusing on specific OR values for individual treatment comparions.

In conclusion, the findings of the current bayesian network meta-analysis indicate that RES or TR may be among the most effective therapeutic approaches for HCC for 5-year survival in both smaller (< 3cm) and larger (3-5cm) lesions. However, evidence was of variable quality, and the majority of evidence came from non randomised studies, which are prone to selection bias and knowledge gaps still exist. For not, at the individual level, selection of strategies should depend on patient and clinical characteristics. To facilitate generation of evidence-based recommendations for HCC therpy, and to standardize treatment approaches, further head-to-head comparisons, especially of resection and ablative therapies, are required from high-quality RCTs, with long follow-up for survival outcomes.

Conflict of interests

The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement

Because this is a meta-analysis, it is not available for Patient Consent. All data in this network meta-analysis have been provided in either the main manuscript or additional file.

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File legends:

Figure 1 Flow chart of search.

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Table 1 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in randomized controlled trials.

〈3cm for 1-year survival

PEI				
10.75 (0.01-29.11)	TR			
0.08 (0-0.42)	1.42 (0-5.94)	MWA		
0.68 (0.28-1.36)	13.24 (0.02-55.15)	**154.8 (1.74-590.10)**	RFA	
0.68 (0.19-1.76)	15.61 (0.02-54.78)	**161.8 (1.39-581.00)**	1.01 (0.40-2.14)	RES

〈3cm for 3-year survival

PEI				
1.29 (0.13-4.99)	TR			
NA	NA	MWA		
0.88 (0.44-1.79)	1.64 (0.20-5.84)	NA	RFA	
0.75 (0.28-1.89)	1.44 (0.14-5.50)	NA	0.86 (0.40-1.68)	RES

〈3cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
0.93 (0.08-3.85)	NA	NA	RFA	
0.49 (0.04-2.02)	NA	NA	0.71 (0.10-2.47)	RES

3-5cm for 1-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.40 (0.64-11.93)	NA	RFA	
NA	1.00 (0-5.00)	NA	0.25 (0-1.47)	RES

3-5cm for 3-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.98 (0.71-15.22)	NA	RFA	
NA	1.14 (0-6.20)	NA	0.24 (0-1.25)	RES

3-5cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	7.64 (0.14-42.49)	NA	RFA	
NA	12.87 (0.02-44.43)	NA	1.05 (0.03-5.33)	RES

≤5cm for 1-year survival

PEI				
0.26 (0.06-0.69)	TR			
0.24 (0.03-0.81)	1.26 (0.14-4.73)	MWA		
0.65 (0.32-1.14)	**3.3 (1.05-8.21)**	4.62 (0.85-15.59)	RFA	
0.42 (0.14-0.98)	2.15 (0.49-6.46)	2.75 (0.52-9.18)	0.65 (0.28-1.31)	RES

≤5cm for 3-year survival

PEI				
0.49 (0.13-1.33)	TR			
1.25 (0.11-5.36)	3.25 (0.24-14.23)	MWA		
0.83 (0.39-1.73)	2.09 (0.81-4.65)	1.71 (0.17-6.61)	RFA	
0.66 (0.23-1.78)	1.69 (0.47-4.87)	1.18 (0.16-4.30)	0.80 (0.36-1.69)	RES

≤5cm for 5-year survival

PEI				
1.51 (0.02-7.71)	TR			
NA	NA	MWA		
0.90 (0.08-3.65)	3.59 (0.14-18.06)	NA	RFA	
0.49 (0.04-2.03)	2.96 (0.05-14.70)	NA	0.72 (0.11-2.48)	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

Table 2 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in all studies

〈3cm for 1-year survival

PEI				
0.56 (0.07-2.13)	TR			
0.55 (0.18-1.29)	1.96 (0.21-7.87)	MWA		
0.69 (0.39-1.13)	2.45 (0.33-8.72)	1.51 (0.60-3.11)	RFA	
0.71 (0.24-1.60)	2.51 (0.26-9.65)	1.55 (0.41-4.10)	1.03 (0.42-2.07)	RES

〈3cm for 3-year survival

PEI				
0.59 (0.15-1.67)	TR			
1.01 (0.45-2.00)	2.35 (0.54-6.80)	MWA		
0.95 (0.59-1.47)	2.21 (0.60-5.76)	1.02 (0.54-1.76)	RFA	
0.80 (0.33-1.68)	1.87 (0.40-5.56)	0.87 (0.31-1.96)	0.85 (0.40-1.62)	RES

〈3cm for 5-year survival

PEI				
1.06 (0.19-3.41)	TR			
0.90 (0.38-1.83)	1.37 (0.23-4.59)	MWA		
0.81 (0.48-1.28)	1.24 (0.25-3.80)	1.00 (0.50-1.77)	RFA	
0.46 (0.18-0.95)	0.72 (0.11-2.48)	0.58 (0.18-1.33)	0.58 (0.24-1.11)	RES

3-5cm for 1-year survival

PEI				
0.21 (0.04-0.56)	TR			
0.60 (0.09-1.94)	3.46 (0.57-11.35)	MWA		
0.50 (0.17-1.13)	**2.92 (1.14-6.65)**	1.25 (0.31-3.46)	RFA	
0.10 (0-0.63)	0.56 (0-3.31)	0.24 (0-1.61)	0.19 (0-1.18)	RES

3-5cm for 3-year survival

PEI				
0.30 (0.03-1.06)	TR			
0.90 (0.08-3.36)	3.48 (0.62-11.64)	MWA		
0.57 (0.10-1.83)	2.37 (0.90-5.53)	1.01 (0.25-2.72)	RFA	
0.09 (0-0.44)	0.36 (0.01-1.73)	**0.15 (0-0.77)**	**0.14 (0.01-0.68)**	RES

3-5cm for 5-year survival

PEI				
6.11 (0-3.02)	TR			
1.88 (0.04-5.54)	13.88 (0.19-50.64)	MWA		
0.79 (0.05-2.64)	7.08 (0.25-26.41)	1.25 (0.18-3.84)	RFA	
1.88 (0.01-3.18)	14.49 (0.05-27.29)	1.79 (0.03-5.39)	0.91 (0.05-4.18)	RES

≤5cm for 1-year survival

PEI				
0.30 (0.11-0.63)	TR			
0.91 (0.41-1.79)	**3.51 (1.78-8.52)**	MWA		
0.78 (0.51-1.13)	**3.01 (1.33-6.15)**	0.95 (0.48-1.67)	RFA	
0.61 (0.26-1.25)	2.35 (0.74-5.96)	0.73 (0.28-1.55)	0.78 (0.37-1.49)	RES

≤5cm for 3-year survival

PEI				
0.52 (0.25-0.96)	TR			
1.03 (0.56-1.77)	2.16 (0.99-4.16)	MWA		
0.92 (0.63-1.32)	**1.93 (1.05-3.29)**	0.94 (0.58-1.44)	RFA	
0.71 (0.37-1.30)	1.50 (0.64-3.08)	0.72 (0.36-1.32)	0.78 (0.44-1.29)	RES

≤5cm for 5-year survival

PEI				
0.71 (0.26-1.57)	TR			
0.90 (0.47-1.58)	1.50 (0.52-3.46)	MWA		
0.85 (0.57-1.22)	1.42 (0.58-2.96)	1.01 (0.60-1.59)	RFA	
0.47 (0.22-0.87)	0.79 (0.24-1.92)	0.56 (0.23-1.14)	**0.56 (0.27-0.99)**	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

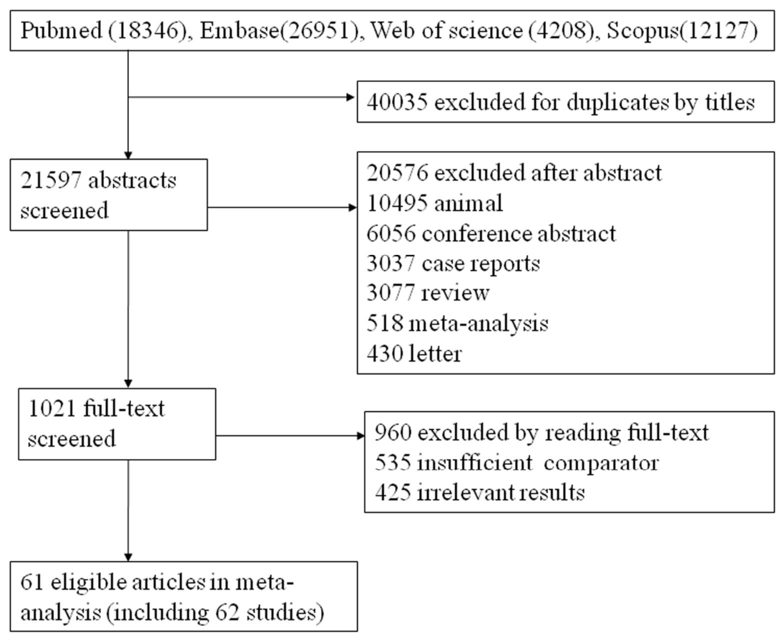

Figure 1 Flow chart of search.

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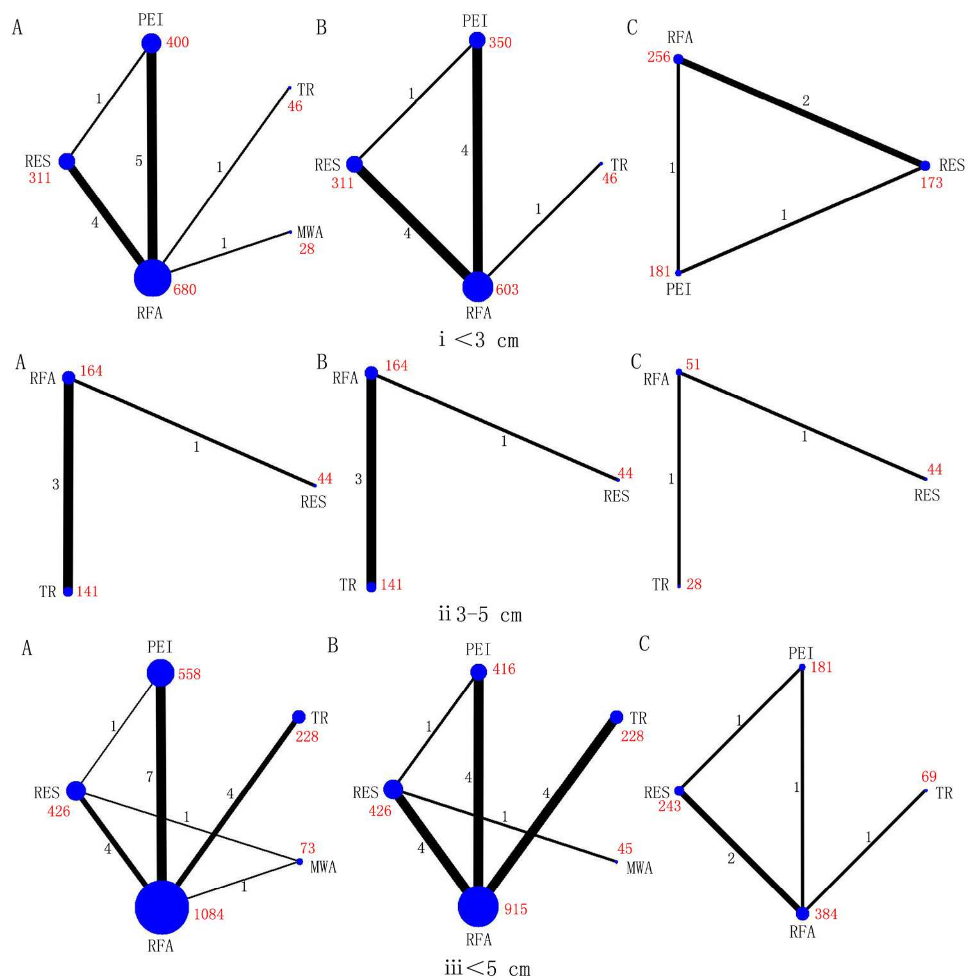

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

227x223mm (300 x 300 DPI)

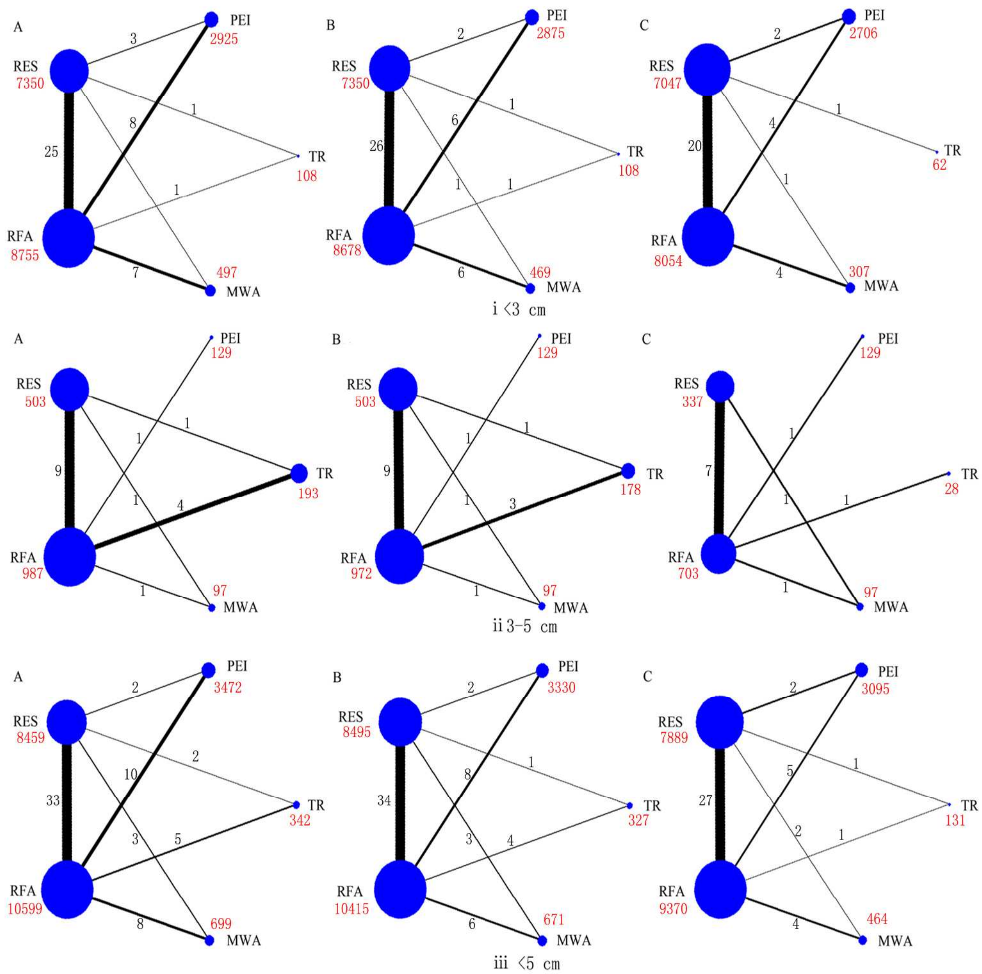

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

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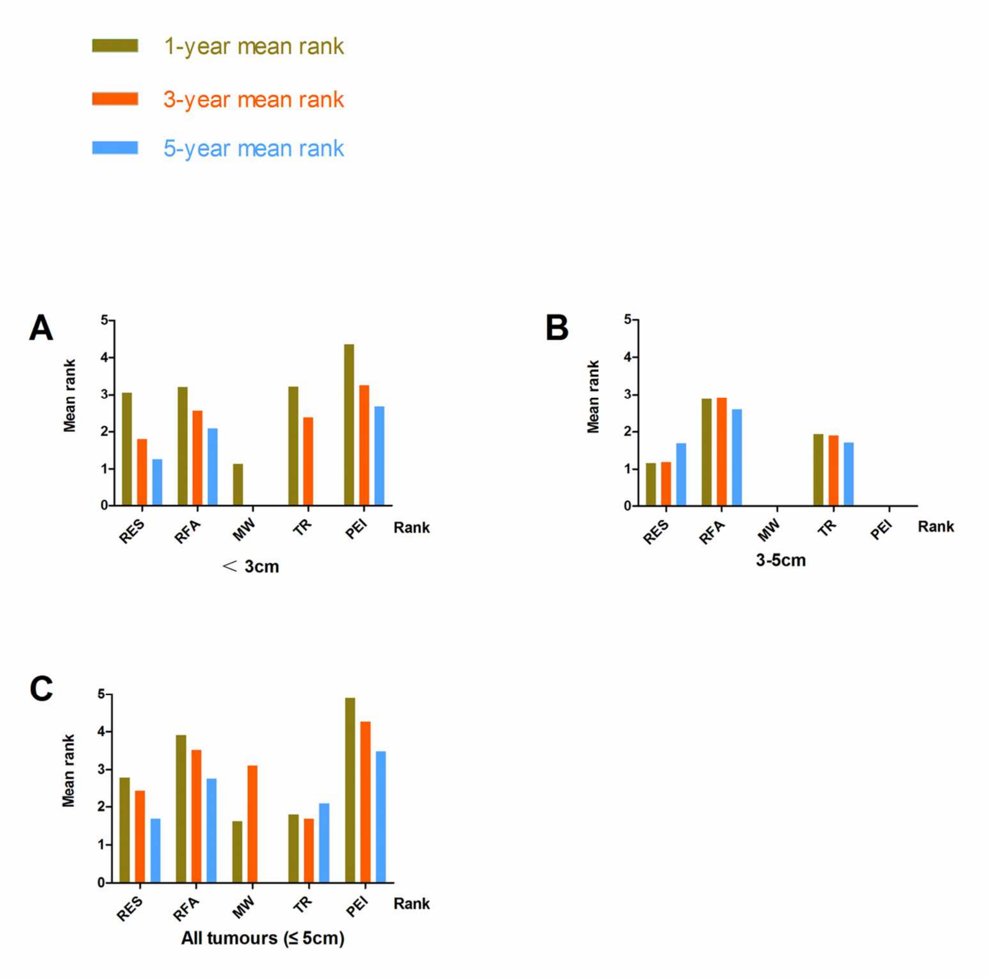

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

118x117mm (300 x 300 DPI)

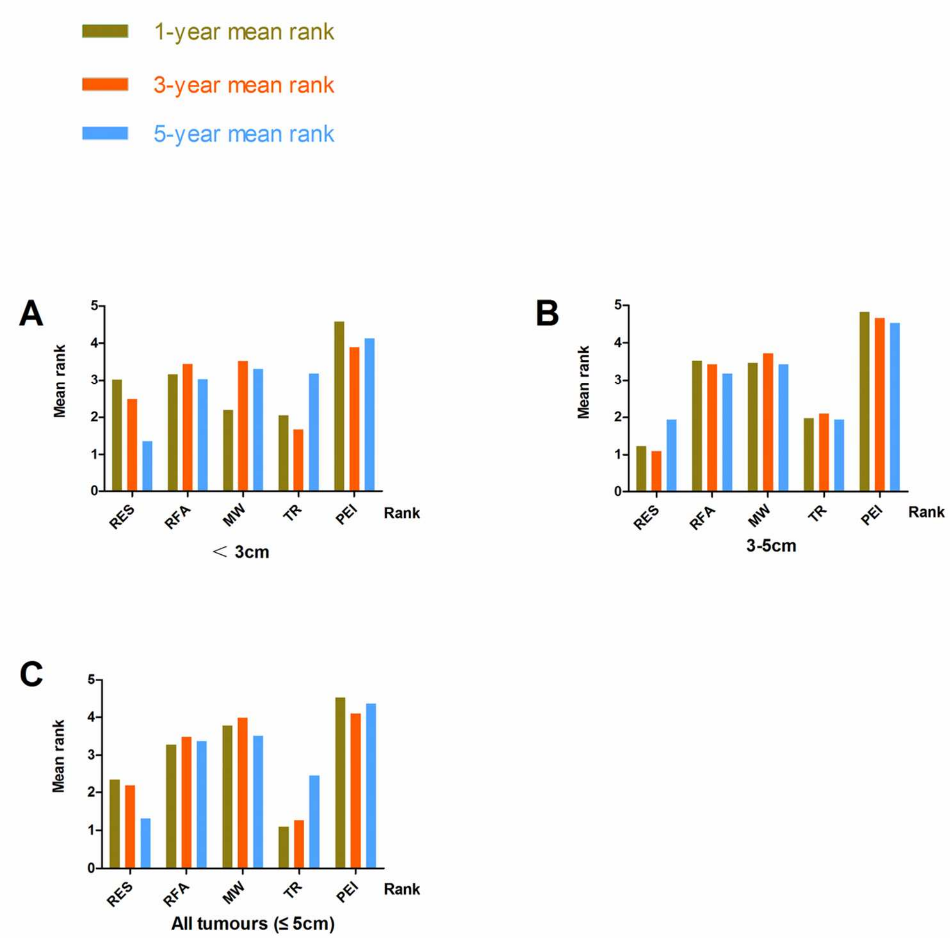

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

118x117mm (300 x 300 DPI)

Text S1.

Search strategy:

Pubmed (1950-present)

1. ("TACE" OR "transarterial chemoembolization")
2. ("RFA" OR "radiofrequency ablation" OR "RF ablation" OR "radiofrequency thermal ablation" OR "RTA")
3. (PEI OR "ethanol injection" OR "ethanol ablation" OR "alcohol ablation")
4. ("microwave ablation" OR "microwave thermal ablation" OR MWA)
5. (liver OR hepato*)
6. (neoplas* OR cancer OR tumor OR tumour OR carcinoma OR oncolog*)
7. 1 OR 2 OR 3 OR 4
8. 5 AND 6 AND 7
9. "Ablation Techniques"[Mesh]
10. "Embolization"[Mesh]
11. "Liver Neoplasms"[Mesh]
12. 9 OR 10
13. 12 AND 11
14. 8 OR 13
15. (resection OR surgery OR hepatectomy)
16. (ablation OR injection OR embolization)
17. 5 AND 6 AND 15 AND 16
18. "Hepatectomy"[Mesh]
19. 12 AND 18 AND 11
20. 17 OR 19
21. 14 OR 20

Embase(1980-present)

1. ' TACE':ab,ti
2. ' transarterial chemoembolization':ab,ti
3. 1 OR 2
4. 'rfa':ab,ti

5. 'radiofrequency ablation':ab,ti
6. 'rf ablation':ab,ti
7. 'radiofrequency thermal ablation':ab,ti
8. 'rta':ab,ti
9. 4 OR 5 OR 6 OR 7 OR 8
10. 'PEI':ab,ti
11. ' ethanol injection ':ab,ti
12. ' ethanol ablation ':ab,ti
13. ' alcohol ablation ':ab,ti
14. 10 OR 11 OR 12 OR 13
15. ' microwave ablation ':ab,ti
16. ' microwave thermal ablation ':ab,ti
17. ' MWA ':ab,ti
18. 15 OR 16 OR 17
19. ' liver':ab,ti
20. ' hepato*':ab,ti
21. 19 OR 20
22. ' neoplas*':ab,ti
23. ' cancer ':ab,ti
24. ' tumor ':ab,ti
25. ' tumour ':ab,ti
26. ' carcinoma ':ab,ti
27. ' oncolog*':ab,ti
28. 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. 3 OR 9 OR 14 OR 18
30. 21 AND 28 AND 29
31. ' resection':ab,ti
32. ' surgery':ab,ti
33. ' hepatectomy':ab,ti
34. 31 OR 32 OR 33
35. ' ablation':ab,ti

36. ' injection':ab,ti
37. ' embolization':ab,ti
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Scoups

1. TITLE-ABS-KEY (“TACE”)
2. TITLE-ABS-KEY (“transarterial chemoembolization”)
3. 1 OR 2
4. TITLE-ABS-KEY ("RFA")
5. TITLE-ABS-KEY (“radiofrequency ablation”)
6. TITLE-ABS-KEY ("RF ablation")
7. TITLE-ABS-KEY ("radiofrequency thermal ablation")
8. TITLE-ABS-KEY ("RTA")
9. 4 OR 5 OR 6 OR 7 OR8
10. TITLE-ABS-KEY (“PEI”)
11. TITLE-ABS-KEY (“ethanol injection”)
12. TITLE-ABS-KEY (“ethanol ablation”)
13. TITLE-ABS-KEY (“alcohol ablation”)
14. 10 OR 11 OR 12 OR 13
15. TITLE-ABS-KEY ("microwave ablation")
16. TITLE-ABS-KEY ("microwave thermal ablation ")
17. TITLE-ABS-KEY ("MWA")
18. 15 OR 16 OR 17
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20. TITLE-ABS-KEY ("hepato*")
21. 19 OR 20
22. TITLE-ABS-KEY ("neoplas*")
23. TITLE-ABS-KEY ("cancer")

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25. TITLE-ABS-KEY ("tumour")
26. TITLE-ABS-KEY ("carcinoma")
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30. 29 AND 21 AND 28
31. TITLE-ABS-KEY ("resection")
32. TITLE-ABS-KEY ("surgery")
33. TITLE-ABS-KEY ("hepatectomy")
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35. TITLE-ABS-KEY ("ablation")
36. TITLE-ABS-KEY ("injection")
37. TITLE-ABS-KEY ("embolization")
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Web of science

1. TS=(ablation)
2. TS=(embolization)
3. 1 OR 2
4. TS=(hepatectomy)
5. TS=(liver neoplasms)
6. 3 AND 4 AND 5
7. TI=(resection)
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9. TI=(hepatectomy)
10. 7 OR 8 OR 9
11. TI=(ablation)

12. TI=(injection)
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22. TI=(carcinoma)
23. TI=(oncolog*)
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28. TI=("transarterial chemoembolization")
29. 27 OR 28
30. TI=(RFA)
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34. TI=(RTA)
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37. TI=("ethanol injection")
38. TI=("ethanol ablation")
39. TI=("alcohol ablation")
40. 36 OR 37 OR 38 OR 39
41. TI=("microwave ablation")
42. TI=("microwave thermal ablation")

43. TI=(MWA)
44. 41 OR 42 OR 43
45. 29 OR 35 OR 40 OR 44
46. 46 AND 17 AND 24
47. 6 OR 25 OR 26 OR 46

Table S1.

Summary of the studies included in the network meta-analysis.

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2002 [19]	Prospective cohort	China	HCC	0.3-2	RFA	15(15)	13/2	61.8 (38-78)	4.1 (2.4-6.0)	NA	0.80(1y)	0.80(1y)	NA
					TR	15(15)	12/3	57.8 (39-72)	4.6 (2.3-7.1)	NA	1.00(1y)	1.00 (1y)	NA
Lencioni 2003 [20]	RCT	Italy	HCC	1.9 ±0.8	RFA	52(69)	36/16	67 ±6 (52-78)	2.8 ±0.6	1.00(1y)	NA	1.00(1y)	15 pain and 10 fever
					PEI	50(73)	30/20	69 ±7.4 (40-82)	2.8 ±0.8	0.96(1y)	NA	0.96(1y)	13 pain and 5 fever
Lin 2004 [21]	RCT	China	HCC	2 ±0.9	RFA	52(69)	35/17	62 ±11	2.9 ±0.8	0.76(3y)	NA	0.35(3y)	1 transient pleural effusion
					PEI	52(67)	34/18	59 ±10	2.8 ±0.8	0.66(3y)	NA	0.17(3y)	1 pain
Vivarelli 2004 [22]	Retrospective cohort	Italy	HCC	2.4	RES	79(92)	57/22	65.2 ±8.2 (43-81)	≤3/3.1-5 (21/58)	0.81(3y)	0.59(3y)	0.65(3y)	NA
					RFA	79(112)	67/12	67.8 ±8.7 (41-88)	≤3/3.1-5 (22/57)	0.50(3y)	0.25(3y)	0.33(3y)	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Cho 2005 [23]	Retrospective cohort	Korea	HCC	0.1-3	RES	61	48/13	57	3.4±1.0	NA	0.77(3y)	0.77(3y)	2 bleeding, 1 intraabdominal abscess, 1 wound infection
					RFA	99	76/23	58	3.1±0.8	NA	0.80(3y)	0.80(3y)	1 chest wall metastasis, 1 cholecystitis, 1 iatrogenic burn, 1 ileus, 1 hepatic infarction
Huang 2005 [25]	RCT	China	HCC	1-4.9	RES	38(42)	27/11	59±11.4	≤2/2.1-3 (24/14)	0.82	NA	0.82	NA
					PEI	38(46)	19/19	63±10.9	≤2/2.1-3 (21/17)	0.45	NA	0.45	NA
Hong 2005 [24]	Retrospective cohort	Korea	HCC	2.9(0.4-4.6)	RES	93	69/24	49.2±9.9	2.5±0.8	0.84(3y)	NA	0.84(3y)	NA
					RFA	55	41/14	59.1±9.6	2.4±0.6	0.73(3y)	NA	0.73(3y)	NA
Lin 2005 [26]	RCT	China	HCC	2.3±1	RFA	62(78)	40/22	61±10	2.5±1	0.74(3y)	NA	0.74(3y)	2 haemothorax, 1 gastric bleeding and perforation
					PEI	62(76)	39/23	60±8	2.3±0.8	0.60(3y)	NA	0.60(3y)	1 pain
Lu 2005 [27]	Retrospective cohort	China	HCC	2.1±1.1	RFA	53(72)	43/10	54.5±11.7 (24-74)	2.6±1.2 (1.0-6.1)	0.38(3y)	NA	0.38(3y)	2 skin burn, 1 puncture wound infection
					MWA	49(98)	44/5	50.1±13.7 (24-74)	2.5±1.2 (0.9-7.2)	0.51(3y)	NA	0.51(3y)	2 puncture wounds, 2 subcapsular hematoma
Montorsi 2005 [28]	Prospective cohort	Italy	HCC	2.1	RES	40	33/7	67±9	<5cm	NA	NA	0.73(3y)	NA
					RFA	58	43/15	67±6		NA	NA	0.60(3y)	NA
Shiina 2005 [29]	RCT	Japan	HCC	3.1(0.6-4.3)	RFA	118(184)	79/39	≤65/>65 (44/74)	≤2/>2 (45/73)	NA	NA	0.61(3y)	1 transient jaundice, 1 skin burn, 1 hepatic infarction, 3 neoplastic seeding

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					PEI	114(188)	87/27	≤65/>65 (41/73)	≤2/>2 (57/57)	NA	NA	0.45(3y)	1 abscess2 neoplastic seeding
Chen 2006 [30]	RCT	China	HCC	2.4±1	RES	90	75/15	49.4±10.9	≤3/3.1-5 (42/48)	0.53	NA	0.53	2 liver failure, 2 gastrointestinal bleeding, 27 ascites
					RFA	71	56/15	51.9±11.2	≤3/3.1-5 (37/34)	0.58	NA	0.58	3 skin burn
Lu 2006 [31]	RCT	China	Early HCC	1.8	RES	54(56)	37/17	49±14	3.2±1.0	NA	NA	0.86 (3y)	3 wound infection, 1 gastrointestinal bleeding
					RFA	51(57)	42/9	55±13	2.7±1.0	NA	NA	0.87 (3y)	1 peritoneal bleeding, 1 neoplastic seeding
Cho 2007 [32]	Retrospective cohort	Korea	HCC	5.7	RES	130(145)	103/27	56.3±8.8	≤2/2.1-3 (43/87)	0.66	NA	0.66	NA
					PEI	249(275)	181/68	57.7±9.7	≤2/2.1-3 (169/80)	0.49	NA	0.49	NA
Gao 2007 [33]	Retrospective cohort	China	HCC	4.6	RES	34(37)	28/6	51.5 (38-67)	2.58±0.41	0.76	NA	0.76	12 fever, 5 ascites
					RFA	53(84)	41/12	57.1 (31-81)	2.45±0.37	0.62	NA	0.62	2 bleeding, 1 fistula, 1 wound infection, 6 fever, 9 ascites
Lupo 2007 [34]	Retrospective cohort	Italy	HCC	2.6	RES	42	33/9	67(28-80)	4.0(3-5)	NA	0.43	0.43	2 urine infection, 1 bilioma, 1 pleural effusion, 1 renal failure, 1 intra-abdominal bleeding
					RFA	60	47/13	68(42-85)	3.65(3-5)	NA	0.32	0.32	2 liver failure, 1 hepatic abscess, 2 pleural effusion, 1 cutaneous metastasis
Zhou 2007 [35]	Retrospective cohort	China	HCC	0.5-5.9	RES	40(42)	35/5	53±13	≤2/2.1-5 (7/33)	NA	NA	0.75	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	47(54)	37/10	57±14	≤2/2.1-5 (8/39)	NA	NA	0.19	NA
Abu-Hilal 2008 [36]	Retrospective cohort	Italy and China	Early HCC	3.6	RES	34	26/8	67	3.8(1.3-5)	NA	0.56	0.56	3 hepatic failure
					RFA	34	27/7	65	3(2-5)	NA	0.56	0.56	1 artero-portal fistula
Brunello 2008 [37]	RCT	Italy	Early HCC	2.2	RFA	70(89)	49/20	70.3±8.1	1.27±0.54	0.60(3y)	NA	0.60(3y)	1 haemoperitoneum 1 right haemothorax
					PEI	69(88)	43/27	69.0±7.7	1.27±0.57	0.58(3y)	NA	0.58(3y)	1 haemoperitoneum 1 death
Guglielmi 2008 [38]	Retrospective cohort	Italy	HCC	2.3	RES	91(113)	73/18	≤65/>65 (47/44)	≤3/3.1-6 (31/60)	0.55	0.43	0.48	33 postoperative complications
					RFA	109(153)	88/21	≤65/>65 (38/71)	≤3/3.1-6 (32/77)	0.28	0.14	0.20	11 postoperative complications
Hiraoka 2008 [39]	Retrospective cohort	Japan	HCC	2.5	RES	59	44/15	62.4±10.6	2.27±0.55	0.59	NA	0.59	1 death, 2 abscess
					RFA	105	76/29	69.4±9.1	1.98±0.52	0.59	NA	0.59	1 biloma, 2 dermatitis
Bu 2009 [45]	Retrospective cohort	China	HCC	2.9(0.5-6)	RES	42(46)	36/6	53.93±10.74	≤3/3.1-5 (14/28)	0.57	0.46	0.50	1 postoperative hemorrhage, 3 pleural effusions, 2 subdiaphragmatic effusion
					RFA	46(54)	40/6	55.89±7.37	≤3/3.1-5 (20/26)	0.50	0.31	0.37	4 pleural effusions, 1 postoperative hemorrhage, 1 skin burn

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Ohmoto 2009 [40]	Retrospective cohort	Japan	HCC	2.8±2	RFA	34(37)	25/9	67 (44-78)	1.6 (0.7-2.0)	0.71	NA	0.71	2 pain, 4 fever, 1 bile duct injury, 1 pleural effusion, 1 skin burns, 1 vagovagal reflex
					MWA	49(56)	41/8	64 (38-75)	1.7 (0.8-2.0)	0.37	NA	0.37	11 pain, 17 fever, 9 bile duct injury, 8 pleural effusion, 5 ascites, 4 skin burns, 2 vagovagal reflex, 2 abscess, 2 intraperitoneal bleeding, 1 hepatic infarction, 1 portal thrombus, 1 biliary peritonitis
Sakaguchi 2009 [41]	Retrospective cohort	Japan	HCC	0.1-5	Laparoscopic /thoracoscopic RFA	249	169/80	65.6±8.9	2.48±0.89	0.57	NA	0.57	1 frequent premature ventricular contractions, 1 liver decompensation
					Laparoscopic /thoracoscopic MWA	142	107/35	64.9±7.8	2.28±0.74	0.63	NA	0.63	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Santambrogio 2009 [42]	Prospective cohort	Italy	HCC	3.2	RES	78	55/23	68±8	2.87±1.21	0.54	NA	0.54	15 extra-hepatic complications
					Laparoscopic RFA	74	59/15	68±7	2.63±1.07	0.41	NA	0.41	14 extra-hepatic complications
Shibata 2009 [43]	RCT	Japan	HCC	2.5±1.2	RFA	43(44)	33/10	69.8±8 (44-87)	1.6±0.5 (0.8-2.6)	0.84(3y)	NA	0.84(3y)	1 pseudoaneurysm

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					TR	46(49)	31/15	67.2±8.9 (45-83)	1.7±0.6 (0.9-3.0)	0.85(3y)	NA	0.85(3y)	1 hepatic infarction
Ueno 2009 [44]	Retrospective cohort	Japan	HCC	3(0.3-7.9)	RES	123(136)	82/41	67(28-85)	2.7±0.1	0.81	0.72	0.80	NA
					RFA	155(209)	100/55	66(40-79)	2.0±0.1	0.38	0.78	0.63	NA
Guo 2010 [46]	Retrospective cohort	China	HCC	2.5	RES	73(155)	57/16	50.0 (17.0-68.0)	≤3/3.1-5 (30/43)	0.27	0.47	0.44	1 postoperative hemorrhage, 5 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	86(211)	63/23	52.5 (26.0-80.0)	≤3/3.1-5 (42/44)	0.33	0.16	0.21	1 postoperative hemorrhage, 1 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Huang 2010 [47]	RCT	China	HCC	3.87	RES	115(144)	85/30	55.91±12.68	≤3/3.1-5 (45/44)	0.82	0.73	0.76	1 hepatic failure, 13 ascites, 5 effusion, 9 bile leakage, 2 postoperative bleeding, 2 gastrointestinal bleeding
					RFA	115(147)	79/36	56.57±14.30	≤3/3.1-5 (57/27)	0.61	0.52	0.55	1 gastric perforation, 2 hemorrhage, 1 malignant seeding, 1 hepatic infarction
Kagawa 2010 [48]	Retrospective cohort	Japan	Early HCC	4.2	RES	55(69)	40/15	66.1±8.4	≤2/2.1-5 (9/46)	0.42	NA	0.42	2 deaths, 1 liver failure, 1 pleural effusion, 1 pneumonia, 2 biliary leakage
					TR	62(79)	39/23	67.5±8.4	≤2/2.1-5 (19/43)	0.29	NA	0.29	1 duodenal perforation, 1 hemothorax
Morimoto	RCT	Japan	HCC	2.7	RFA	18(25)	12/6	73 (48-84)	3.7±0.6	NA	0.78(3y)	0.78(3y)	5 pain, 2 pleural effusion

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
2010 [49]					TR	19(21)	15/4	70 (57-78)	3.6 ±0.7	NA	0.95(3y)	0.95(3y)	1 pain, 1 pleural effusion
Azab 2011 [50]	RCT	Egypt	HCC	1.5	RFA	30(33)	75/15	46-77	<5cm	NA	NA	0.90	5 superficial burn, 17 transient pain, 3 portal vein thrombosis, 7 fever, 1 ascites
					PEI	30(32)				NA	NA	0.83	2 portal vein thrombosis, 3 fever, 3 ascites
Giorgio 2011 [51]	RCT	Italy	HCC	1.8	RFA	142	105/37	70 ±2 (68-74)	2.34 ±0.45 (1.1-3)	0.70	NA	0.70	1 major complication
					PEI	143	102/41	72 ±6 (68-79)	2.27 ±0.48 (1.3-2.9)	0.68	NA	0.68	3 major complication
Hung 2011 [52]	Retrospective cohort	China	Early HCC	3.5 ±2	RES	229	184/45	60.07 ±12.56	2.88 ±1.06	0.77	NA	0.77	NA
					RFA	190	121/69	67.42 ±11.45	2.37 ±0.92	0.67	NA	0.67	NA
Nishikawa 2011 [53]	Retrospective cohort	Japan	HCC	3.3	RES	69	50/19	67.4 ±9.7	2.68 ±0.49	0.74	NA	0.74	2 bile leakage, 2 ascites, 1 acute respiratory distress syndrome, 1 gastrointestinal bleeding
					RFA	162	95/67	68.4 ±8.7	1.99 ±0.62	0.63	NA	0.63	1 biloma, 1 ascites, 1 intra-abdominal bleeding
Yun 2011 [54]	Retrospective cohort	Korea	HCC	3.5(0.1-9.1)	RES	215	171/44	51.7 ±9.7	2.1 ±0.5	0.94	NA	0.94	NA
					RFA	255	197/58	57.0 ±9.9	2.1 ±0.5	0.87	NA	0.87	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2011 [55]	Retrospective cohort	China	HCC	0.5-3.5	RES	103(117)	78/25	56.4±15.2	<5cm	NA	NA	0.35(3y)	12 wound infection, 5 postoperative hemorrhage, 2 hepatic failure, 15 pleural effusions, 6 pleural effusions
					RFA	85(106)	62/23	58.5±12.9	<5cm	NA	NA	0.39(3y)	2 gallbladder cardiac reflex, 4 postoperative hemorrhage, 3 pleural effusions
Feng 2012 [57]	RCT	China	HCC	3	RES	84(116)	75/9	47 (18-76)	2.6±0.8	0.62(3y)	NA	0.62(3y)	7 pleural effusion, 3 pneumonia, 1 effusion plus infection, 3 wound infection or dehiscence, 1 biliary fistula, 2 abdominal bleeding, 1 pneumothorax or hemothorax
					RFA	84(120)	79/5	51 (24-83)	2.4±0.6	0.55(3y)	NA	0.55(3y)	5 pleural effusion, 1 liver abscess, 2 abdominal bleeding
Peng 2012 [58]	Retrospective cohort	China	Recurrent HCC	4.9	RES	74	65/9	51.5±12.1 (24-75)	1.1±0.5 (0.8-2.0)	0.62	NA	0.62	1 liver failure, 2 gastrointestinal bleeding, 1 peritoneal bleeding, 1 intestinal obstruction, 1 spontaneous bacterial peritonitis, 1 persistent jaundice, 31 ascites
					RFA	71	63/8	53.1±12.1 (28-74)	1.2±0.6 (0.9-2.0)	0.72	NA	0.72	1 gastrointestinal bleeding, 1 persistent jaundice, 12 ascites

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Peng 2012 [59]	RCT	China	Recurrent HCC	3.3±1.8	RFA	70(76)	55/15	55.1±9.5 (22-75)	≤3/3.1-5 (46/24)	NA	0.17	0.36	1 persistent jaundice, 1 ascites, 22 fever, 45 pain, 4 vomiting
					TR	69(74)	59/9	57.5±10.0 (19-75)	≤3/3.1-5 (41/28)	NA	0.39	0.46	1 liver failure, 1 ascites, 27 fever, 50 pain, 42 vomiting
Signoriello 2012 [60]	Retrospective cohort	Italy	HCC	0.1-9	RES	34(44)	30/4	62±7	≤3/3.1-5/>5.1 (13/9/4)	NA	NA	0.29	NA
					RFA	50(74)	40/10	68±7	≤3/3.1-5/>5.1 (24/11/7)	NA	NA	0.15	NA
					PEI	256(349)	188/68	67±8	≤3/3.1-5/>5.1 (143/43/12)	NA	NA	0.20	NA
a. Wang 2012 [61]	Retrospective cohort	China	Early HCC	2.5	RES	52	38/14	≤60 (35)	NA	NA	NA	0.92	NA
					RFA	91	60/31	≤60 (40)		NA	NA	0.73	NA
b. Wang 2012 [62]	Retrospective cohort	China	Early HCC	2.5	RES	208	168/40	≤60 (113)	≤2/2.1-5 (6/202)	NA	NA	0.77	NA
					RFA	254	161/93	≤60 (85)	≤2/2.1-5 (60/194)	NA	NA	0.57	NA
Desiderio 2013 [62]	Retrospective cohort	Italy	HCC	4.3(2.3-5)	RES	52(94)	37/15	65.6±4.8	≤3	0.46	NA	0.46	2 hepatic failure, 1 biliary fistula, 2 hemoperitoneum, 9 ascites
					RFA	44(81)	35/9	64.4±6.5		0.36	NA	0.36	6 pain, 7 fever
Ding 2013 [63]	Retrospective cohort	China	HCC	2.3±1.3	RFA	85(98)	68/17	58.64±8.52 (40-77)	2.38±0.81 (1.0-4.8)	0.82(3y)	NA	0.82(3y)	1 frequent premature ventricular contractions, 1 liver decompensation

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					MWA	113(131)	85/28	59.06 ±11.68 (30-86)	2.55 ±0.89 (0.8-5.0)	0.78(3y)	NA	0.78(3y)	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Guo 2013 [64]	Retrospective cohort	China	HCC	2.7	RES	102(129)	94/8	51.5(18-75)	≤3/3.1-5 (75/27)	NA	NA	0.63	5 postoperative hemorrhage, 3 bile leak, 4 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	94(125)	78/16	56(19-75)	≤3/3.1-5 (62/32)	NA	NA	0.50	1 postoperative hemorrhage, 2 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Hasegawa 2013 [65]	Retrospective cohort	Japan	HCC	2.2	RES	5361(6461)	3967/1394	66 (48-77)	2.3 (1.2-3)	0.71	NA	0.71	NA
					RFA	5548(7412)	3569/1979	69 (52-80)	2 (1-3)	0.61	NA	0.61	NA
					PEI	2059(2836)	1303/756	69 (52-80)	1.7 (1-3)	0.56	NA	0.56	NA
Iida 2013 [66]	Retrospective cohort	Japan	HCC	0.1-7.5	Laparoscopic RFA	18(27)	NA	73.5 ±4.0	2.1 ±0.5	0.78	NA	0.78	1 abscess
					Laparoscopic MWA	40(56)		70.1 ±6.6	2.0 ±0.9	0.78	NA	0.78	1 abscess
Imai 2013 [67]	Retrospective cohort	Japan	HCC	4.1	RES	101	75/26	63.3 ±9.7	2.14 ±0.55	0.87	NA	0.87	NA
					RFA	82	46/36	67.6 ±8.5	1.87 ±0.50	0.60	NA	0.60	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Kim 2013 [68]	Retrospective cohort	Korea	Early HCC	0.1-4.2	RES	47	36/11	58.8±10.7	3.66±0.76	NA	0.85(3y)	0.85(3y)	2 pleural effusion, 2 pneumonia, 1 hepatic failure, 1 hepatic abscess, 1 mechanical ileus
					TR	37	31/6	61.7±11.1	3.46±0.75	NA	0.78(3y)	0.78(3y)	1 bile duct dilatation
Lai 2013 [69]	Retrospective cohort	China	HCC	2.9±1.5	RES	80	55/25	60.8±9.9	2.9±1.1	0.71	NA	0.71	NA
					RFA	31	19/12	63.1±12.8	1.8±0.6	0.84	NA	0.84	NA
Lin 2013 [70]	Retrospective cohort	China	Early HCC	3.4	RFA	658	393/265	64.7±10.5	2.4±1.1 (0.8-9.5)	0.60	0.50	0.55	NA
					PEI	378	243/135	63.5±12.1	2.0±0.9 (0.4-7.0)	0.50	0.28	0.40	NA
Peng 2013 [71]	RCT	China	HCC	0.6-5.2	RFA	95(133)	71/24	55.3±13.3	3.39±1.35	NA	0.59(3y)	0.59(3y)	51 pain, 26 fever, 29 vomiting, 4 ascites, 2 pleural effusion, 1 skin burn, 1 abdominal infection, 1 small intestinal obstruction
					TR	94(137)	75/19	53.3±11	3.47±1.44	NA	0.67(3y)	0.67(3y)	57 pain, 33 fever, 40 vomiting, 5 ascites, 3 pleural effusion, 1 skin burn, 1 bile duct stenosis, 1 gastric hemorrhage
Tohme 2013 [72]	Retrospective cohort	America	Early HCC	2.4	RES	50(62)	31/19	66.3±1	3.07±1.17	0.48	NA	0.48	3 pleural effusion, 1 pneumonia, 1 myocardial infarction, 2 biloma, 2 ileus, 1 ascites, 1 hyperbilirubinaemia >6, 1 renal insufficiency, 2 encephalopathy

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	60(75)	38/22	65.6±12	2.36±0.94	0.35	NA	0.35	1 oesophagitis, 3 encephalopathy, 1 cholangitis, 2 ascites, 1 renal insufficiency, 1 pneumonia
Wong 2013 [73]	Retrospective cohort	China	Early HCC	0.1-5	RES	46	30/16	55.1±12	2.1±0.6	0.85	NA	0.85	2 fever, 1 increased serum alanine aminotransferase level, 2 atelectasis, 2 biloma
					RFA	36	18/18	63.5±13	1.9±0.6	0.72	NA	0.72	None
Zhang 2013 [74]	Retrospective cohort	China	HCC	2.2±1	RFA	78(97)	64/14	54±10.5 (30-80)	≤3/3.1-5 (47/31)	0.43	0.39	0.41	1 persistent jaundice, 1 biliary fistula
					MWA	77(105)	67/10	54±9.5 (26-76)	≤3/3.1-5 (36/41)	0.58	0.29	0.39	1 hemothorax and intrahepatic hematoma, 1 peritoneal hemorrhage
Abdelaziz 2014 [75]	RCT	Egypt	Early HCC	2.3	RFA	45(52)	31/14	56.8±7.3	2.95±1.03	0.68(1y)	NA	0.68(1y)	2 subcapsular hematoma, 1 thigh burn, 2 pleural effusion
					MWA	66(76)	48/18	53.6±5	2.9±0.97	0.96(1y)	NA	0.96(1y)	1 subcapsular hematoma, 1 abdominal wall skin burn
Shi 2014 [76]	Retrospective cohort	China	HCC	3.8	RES	107(126)	87/20	54.5±9.9	≤3/3.1-5 (37/54)	0.73	0.57	0.60	NA
					MWA	117(143)	93/24	56.6±9.2	≤3/3.1-5 (40/56)	0.65	0.52	0.52	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Yang 2014 [77]	Retrospective cohort	Korea	HCC	0.1-7	RES	52	38/14	55.7 ±10.6	≤2/2.1-5 (21/31)	0.94	NA	0.94	2 pneumonia, 1 wound infection, 1 biliary anastomotic leak, 1 portal vein thrombosis, 1 nausea, 1 delirium, 4 ascites
					RFA	79	59/20	57.2 ±9.2	≤2/2.1-5 (36/43)	0.86	NA	0.86	1 vomiting, 1 ascites, 6 abdominal pain, 2 nausea, 1 sinus bradycardia
Zhang 2014 [78]	Retrospective cohort	China	Recurrent HCC	2.7	RES	27(29)	25/2	47 ±13	3.2 ±1.0	NA	NA	0.63	NA
					MWA	39(46)	37/2	52 ±13	2.7 ±1.1	NA	NA	0.62	NA
Pompili 2015 [79]	Retrospective cohort	Italy	Early HCC	2.8	RFA	136	75/61	68 (41-85)	1.8 (1-2)	0.63	NA	0.63	2 ascites, 1 pleural effusion, 1 hemobilia
					PEI	108	90/18	68.5 (34-86)	1.95 (0.8-2)	0.65	NA	0.65	1 hemobilia, 1 portal vein thrombosis
Xu 2015 [80]	RCT	China	HCC	0.1-3	Laparoscopic RES	45	34/11	58.3 ±3.1 (26-78)	3.6 ±0.7 (1-5)	NA	0.38(3y)	0.38(3y)	3 bile leakage, 3 pleural effusion, 2 postoperative hemorrhage
					MWA	45	32/13	57.9 ±3.4 (27-76)	3.8 ±0.9 (2-5)	NA	0.33(3y)	0.33(3y)	1 bile leakage, 1 pleural effusion, 1 postoperative hemorrhage

HCC: hepatocellular carcinoma;

BCLC: Barcelona Clinic Liver Cancer;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

RCT: randomized controlled trial;

NA: not available.

Table S2.
Quality assessment of included studies using GRADE framework.

Intervention/Comparator	Illustrative comparative risks* (per 1000, 95% CI)		Relative effect of survival time (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Comparator Assumed survival risk	Corresponding survival risk with intervention			
1-year OS rate					
RES/MWA	923	984 (932 to 997)	**OR 5.25 (1.15 to 23.97)**	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	947	944 (902 to 968)	OR 0.94 (0.52 to 1.71)	990 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	835	802 (674 to 889)	OR 0.80 (0.41 to 1.58)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	944	963 (906 to 1000)	OR 1.02 (0.96 to 1.09)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	932	945 (931 to 956)	OR 1.25 (0.99 to 1.60)	5006 (30 studies)	⊕⊕⊕⊕ high

RES/TR	939	904 (765 to 965)	OR 0.61 (0.21 to 1.79)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	938	802 (310 to 978)	OR 0.27 (0.03 to 2.90)	31 (1 study)	⊕⊕⊖⊖ low
3-year OS rate					
RES/MWA	712	734 (623 to 822)	OR 1.12 (0.67 to 1.87)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	736	779 (717 to 828)	OR 1.26 (0.91 to 1.73)	987 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	499	536 (421 to 645)	OR 1.16 (0.73 to 1.83)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	729	748 (657 to 822)	OR 1.10 (0.71 to 1.71)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	785	851 (823 to 875)	**OR 1.57 (1.28 to 1.93)**	15906 (30 studies)	⊕⊕⊕⊖ moderate
RES/TR	798	760 (618 to 860)	OR 0.80 (0.41 to 1.55)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	737	611 (516 to 704)	OR 0.56 (0.38 to 0.85)	454 (4 studies)	⊕⊕⊕⊖ moderate
5-year OS rate					
RES/MWA	545	607 (492 to 712)	OR 1.29 (0.81 to 2.07)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	545	609 (442 to 756)	OR 1.30 (0.66 to 2.58)	687 (4 studies)	⊕⊕⊖⊖ low

RES/PEI	293	436 (334 to 545)	**OR 1.87 (1.21 to 2.90)**	519 (3 studies)	⊕⊕⊕⊖ moderate
RFA/PEI	533	496 (368 to 624)	OR 0.86 (0.51 to 1.45)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	601	744 (705 to 779)	**OR 1.93 (1.59 to 2.34)**	15154 (25 studies)	⊕⊕⊕⊖ moderate
RES/TR	290	419 (251 to 607)	OR 1.76 (0.82 to 3.78)	117 (1 study)	⊕⊕⊖⊖ low
RFA/TR	464	356 (222 to 523)	OR 0.64 (0.33 to 1.27)	139 (1 study)	⊕⊕⊕⊖ moderate

The absolute and relative risk of survival with treatments*. GRADE: Grading of Recommendations, Assessment, Development and Evaluation. *The results presented in the Table S1 were built around the assumption of a consistent relative effect. The implications of this effect for populations were considered at different baseline risks. Based on the assumed risks, corresponding risks after an intervention were calculated using the meta-analytic risk ratio.

Table S3.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in RCT.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	12			10			4		
RES		2	3.06		1	1.80		1	1.25
RFA		3	3.21		3	2.56		2	2.08
MWA		1	1.14		NA	NA		NA	NA
TR		4	3.22		2	2.38		NA	NA
PEI		5	4.36		4	3.26		3	2.68

3-5cm	4			4			2		
RES		1	1.17		1	1.19		1	1.69
RFA		3	2.88		3	2.91		3	2.60
MWA		NA	NA		NA	NA		NA	NA
TR		2	1.94		2	1.90		2	1.71
PEI		NA	NA		NA	NA		NA	NA
All tumours (≤ 5cm)	18			14			5		
RES		3	2.78		2	2.43		1	1.68
RFA		4	3.91		3	3.52		3	2.75
MWA		1	1.62		4	3.10		NA	NA
TR		2	1.79		1	1.68		2	2.09
PEI		5	4.90		5	4.27		4	3.48

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S4.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in all studies.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	44			42			31		
RES		3	3.02		2	2.49		1	1.35
RFA		4	3.16		3	3.44		2	3.03
MWA		2	2.19		4	3.52		4	3.31
TR		1	2.05		1	1.66		3	3.18

PEI		5	4.58		5	3.89		5	4.13
3-5cm	17			16			11		
RES		1	1.23		1	1.10		1	1.93
RFA		4	3.52		3	3.43		3	3.18
MWA		3	3.46		4	3.72		4	3.43
TR		2	1.97		2	2.10		2	1.94
PEI		5	4.82		5	4.66		5	4.53
All tumours (≤ 5cm)	62			57			40		
RES		2	2.34		2	2.18		1	1.32
RFA		3	3.27		3	3.48		3	3.36
MWA		4	3.78		4	3.98		4	3.51
TR		1	1.10		1	1.27		2	2.45
PEI		5	4.52		5	4.10		5	4.36

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S5.
Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	1.01 (0.40-2.14)	0.98 (0.77-1.26)
MWA vs RES	**161.8 (1.39-581.0)**	NA
TR vs RES	15.61 (0.02-54.78)	NA
PEI vs RES	0.68 (0.19-1.76)	1.03 (0.54-1.94)

MWA vs RFA	**154.8 (1.74-590.1)**	1.42 (0.63-3.19)
TR vs RFA	13.24 (0.02-55.15)	1.00 (0.56-1.80)
PEI vs RFA	0.68 (0.28-1.36)	0.97 (0.78-1.19)
TR vs MWA	1.42 (0-5.94)	NA
PEI vs MWA	**0.08 (0-0.42)**	NA
PEI vs TR	10.75 (0.01-29.11)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.86 (0.40-1.68)	0.92 (0.71-1.19)
MWA vs RES	NA	NA
TR vs RES	1.44 (0.14-5.50)	NA
PEI vs RES	0.75 (0.28-1.89)	1.21 (0.59-2.15)
MWA vs RFA	NA	NA
TR vs RFA	1.64 (0.20-5.84)	1.01 (0.55-1.87)
PEI vs RFA	0.88 (0.44-1.79)	0.91 (0.71-1.17)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.29 (0.13-4.99)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.71 (0.10-2.47)	0.93 (0.62-1.37)
MWA vs RES	NA	NA
TR vs RES	NA	NA
PEI vs RES	0.49 (0.04-2.02)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	NA	NA
PEI vs RFA	0.93 (0.08-3.85)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S6.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in

RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.25 (0-1.47)	0.89 (0.45-1.77)
MWA vs RES	NA	NA
TR vs RES	1.00 (0-5.0)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.40 (0.64-11.93)	1.10 (0.78-1.55)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.24 (0-1.25)	0.70 (0.34-1.45)
MWA vs RES	NA	NA
TR vs RES	1.14 (0-6.20)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.98 (0.71-15.22)	1.29 (0.87-1.89)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
5-year OS rate for treatment vs reference		
RFA vs RES	1.05 (0.03-5.33)	0.71 (0.32-1.57)
MWA vs RES	NA	NA
TR vs RES	12.87 (0.02-44.43)	NA
PEI vs RES	NA	NA

MWA vs RFA	NA	NA
TR vs RFA	7.64 (0.14-42.49)	1.93 (0.53-7.06)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S7.

Survival rates (1-year, 3-year and 5-year) for lesion (≤5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.65 (0.28-1.31)	0.96 (0.77-1.20)
MWA vs RES	2.75 (0.52-9.18)	0.98 (0.54-1.78)
TR vs RES	2.15 (0.49-6.46)	NA
PEI vs RES	**0.42 (0.14-0.98)**	1.03 (0.54-1.94)
MWA vs RFA	4.62 (0.85-15.59)	1.42 (0.63-3.19)
TR vs RFA	**3.3 (1.05-8.21)**	1.09 (0.84-1.43)
PEI vs RFA	0.65 (0.32-1.14)	0.95 (0.80-1.14)
TR vs MWA	1.26 (0.14-4.73)	NA
PEI vs MWA	**0.24 (0.03-0.81)**	NA
PEI vs TR	**0.26 (0.06-0.69)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.80 (0.36-1.69)	0.87 (0.69-1.10)
MWA vs RES	1.18 (0.16-4.30)	0.88 (0.39-1.98)
TR vs RES	1.69 (0.47-4.87)	NA
PEI vs RES	0.66 (0.23-1.78)	1.12 (0.59-2.15)
MWA vs RFA	1.71 (0.17-6.61)	NA
TR vs RFA	2.09 (0.81-4.65)	1.20 (0.90-1.60)

PEI vs RFA	0.83 (0.39-1.73)	0.84 (0.66-1.07)
TR vs MWA	3.25 (0.24-14.23)	NA
PEI vs MWA	1.25 (0.11-5.36)	NA
PEI vs TR	0.49 (0.13-1.33)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.11-2.48)	0.85 (0.61-1.17)
MWA vs RES	NA	NA
TR vs RES	2.96 (0.05-14.7)	NA
PEI vs RES	0.49 (0.04-2.03)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	3.59 (0.14-18.06)	1.30 (0.70-2.41)
PEI vs RFA	0.90 (0.08-3.65)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.51 (0.02-7.71)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S8.

Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		

RFA vs RES	1.03 (0.42-2.07)	1.00(0.95-1.05)
MWA vs RES	1.55 (0.41-4.10)	1.00(0.53-1.89)
TR vs RES	2.51 (0.26-9.65)	1.00(0.56-1.80)
PEI vs RES	0.71 (0.24-1.60)	1.00 (0.93-1.07)
MWA vs RFA	1.51 (0.60-3.11)	1.02 (0.85-1.23)
TR vs RFA	2.45 (0.33-8.72)	1.00(0.56-1.80)
PEI vs RFA	0.69 (0.39-1.13)	0.99 (0.93-1.06)
TR vs MWA	1.96 (0.21-7.87)	NA
PEI vs MWA	0.55 (0.18-1.29)	NA
PEI vs TR	0.56 (0.07-2.13)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.85 (0.40-1.62)	**0.94 (0.90-0.99)**
MWA vs RES	0.87 (0.31-1.96)	0.96 (0.49-1.87)
TR vs RES	1.87 (0.40-5.56)	1.17 (0.67-2.04)
PEI vs RES	0.80 (0.33-1.68)	1.00 (0.71-1.40)
MWA vs RFA	1.02 (0.54-1.76)	1.00 (0.82-1.22)
TR vs RFA	2.21 (0.60-5.76)	1.01 (0.55-1.87)
PEI vs RFA	0.95 (0.59-1.47)	0.97 (0.90-1.03)
TR vs MWA	2.35 (0.54-6.80)	NA
PEI vs MWA	1.01 (0.45-2.00)	NA
PEI vs TR	0.59 (0.15-1.67)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.58 (0.24-1.11)	**0.86 (0.81-0.90)**
MWA vs RES	0.58 (0.18-1.33)	0.89 (0.44-1.79)
TR vs RES	0.72 (0.11-2.48)	0.69 (0.34-1.42)
PEI vs RES	**0.46 (0.18-0.95)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.00 (0.50-1.77)	1.02 (0.78-1.33)
TR vs RFA	1.24 (0.25-3.80)	NA
PEI vs RFA	0.81 (0.48-1.28)	**0.92 (0.85-0.99)**
TR vs MWA	1.37 (0.23-4.59)	NA
PEI vs MWA	0.90 (0.38-1.83)	NA

PEI vs TR	1.06 (0.19-3.41)	NA

Table S9.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.19 (0-1.18)	0.96 (0.78-1.17)
MWA vs RES	0.24 (0-1.61)	NA
TR vs RES	0.56 (0-3.31)	1.02 (0.55-1.88)
PEI vs RES	**0.10 (0-0.63)**	NA
MWA vs RFA	1.25 (0.31-3.46)	0.98 (0.49-1.95)
TR vs RFA	**2.92 (1.14-6.65)**	1.11 (0.80-1.54)
PEI vs RFA	0.50 (0.17-1.13)	0.89 (0.66-1.20)
TR vs MWA	3.46 (0.57-11.35)	NA
PEI vs MWA	0.60 (0.09-1.94)	NA
PEI vs TR	**0.21 (0.04-0.56)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	**0.14 (0.01-0.68)**	**0.78 (0.62-0.98)**
MWA vs RES	**0.15 (0-0.77)**	1.02 (0.57-1.81)
TR vs RES	0.36 (0.01-1.73)	0.92 (0.48-1.75)
PEI vs RES	**0.09 (0-0.44)**	NA
MWA vs RFA	1.01 (0.25-2.72)	0.60 (0.26-1.36)
TR vs RFA	2.37 (0.90-5.53)	1.29 (0.87-1.89)
PEI vs RFA	0.57 (0.10-1.83)	0.71 (0.50-1.00)
TR vs MWA	3.48 (0.62-11.64)	NA
PEI vs MWA	0.90 (0.08-3.36)	NA
PEI vs TR	0.30 (0.03-1.06)	NA
5-year OS rate for treatment vs reference		

RFA vs RES	0.91 (0.05-4.18)	**0.62 (0.45-0.85)**
MWA vs RES	1.79 (0.03-5.39)	0.90 (0.48-1.69)
TR vs RES	14.49 (0.05-27.29)	NA
PEI vs RES	1.88 (0.01-3.18)	NA
MWA vs RFA	1.25 (0.18-3.84)	0.57 (0.21-1.51)
TR vs RFA	7.08 (0.25-26.41)	2.36 (0.66-8.37)
PEI vs RFA	0.79 (0.05-2.64)	**0.56 (0.37-0.84)**
TR vs MWA	13.88 (0.19-50.64)	NA
PEI vs MWA	1.88 (0.04-5.54)	NA
PEI vs TR	6.11 (0-3.02)	NA

Table S10.

Survival rates (1-year, 3-year and 5-year) for lesion (≤ 5cm) treatment comparisons estimated by direct, indirect and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.78 (0.37-1.49)	0.99 (0.95-1.04)
MWA vs RES	0.73 (0.28-1.55)	0.95 (0.71-1.27)
TR vs RES	2.35 (0.74-5.96)	1.04 (0.70-1.55)
PEI vs RES	0.61 (0.26-1.25)	1.01 (0.74-1.39)
MWA vs RFA	0.95 (0.48-1.67)	1.01 (0.85-1.21)
TR vs RFA	**3.01 (1.33-6.15)**	1.10 (0.85-1.43)
PEI vs RFA	0.78 (0.51-1.13)	0.98 (0.93-1.05)
TR vs MWA	**3.51 (1.78-8.52)**	0.91 (0.70-1.18)
PEI vs MWA	0.91 (0.41-1.79)	NA
PEI vs TR	**0.30 (0.11-0.63)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.78 (0.44-1.29)	**0.93 (0.89-0.98)**
MWA vs RES	0.72 (0.36-1.32)	0.96 (0.69-1.32)

TR vs RES	1.50 (0.64-3.08)	1.06 (0.69-1.61)
PEI vs RES	0.71 (0.37-1.30)	**0.93 (0.86-1.00)**
MWA vs RFA	0.94 (0.58-1.44)	0.95 (0.78-1.16)
TR vs RFA	**1.93 (1.05-3.29)**	1.20 (0.90-1.60)
PEI vs RFA	0.92 (0.63-1.32)	0.95 (0.89-1.01)
TR vs MWA	2.16 (0.99-4.16)	NA
PEI vs MWA	1.03 (0.56-1.77)	NA
PEI vs TR	**0.52 (0.25-0.96)**	NA
5-year OS rate for treatment vs reference		
RFA vs RES	**0.56 (0.27-0.99)**	**0.84 (0.80-0.89)**
MWA vs RES	0.56 (0.23-1.14)	0.90 (0.61-1.31)
TR vs RES	0.79 (0.24-1.92)	0.69 (0.34-1.42)
PEI vs RES	**0.47 (0.22-0.87)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.01 (0.60-1.59)	0.97 (0.75-1.25)
TR vs RFA	1.42 (0.58-2.96)	1.30 (0.70-2.41)
PEI vs RFA	0.85 (0.57-1.22)	**0.91 (0.84-0.98)**
TR vs MWA	1.50 (0.52-3.46)	NA
PEI vs MWA	0.90 (0.47-1.58)	NA
PEI vs TR	0.71 (0.26-1.57)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S11.

Posterior summaries from random effects consistency and inconsistency models for small lesion (<3cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.55	0.21	(0.15-1.00)	0.38	0.23	(0.02-0.88)
τ	11.06	88.80	(1.00-43.58)	4020	78840	(1.28-2366.00)
resdev	90.04	13.04	(66.16-117.10)	94.65	12.94	(70.06-120.70)
pD	59.96			57.5		
DIC	402.44			404.59		
3-year OS rate for treatment vs reference						
σ	0.59	0.14	(0.34-0.88)	0.6	0.14	(0.36-0.91)
τ	3.74	10.43	(1.29-8.74)	3.29	1.92	(1.21-8.05)
resdev	92.02	14.19	(66.64-122.10)	90.7	13.92	(65.64-120.00)
pD	70.71			71.74		
DIC	517.72			517.43		
5-year OS rate for treatment vs reference						
σ	0.53	0.12	(0.32-0.80)	0.55	0.13	(0.34-0.84)
τ	4.19	2.29	(1.57-9.74)	3.82	2.02	(1.42-8.83)
resdev	63.99	11.47	(43.52-88.24)	63.55	11.37	(43.39-87.90)
pD	54.24			54.99		
DIC	411.73			412.03		

Table S12.
Posterior summaries from random effects consistency and inconsistency models for lesion (3-5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.28	0.25	(0.01-0.92)	0.38	0.34	(0.02-1.28)
τ	42220	1.30E+06	(1.19-19650.00)	19500.00	720600.00	(0.62-4178.00)

resdev	28.90	6.96	(17.25-44.41)	32.18	7.36	(19.64-48.32)
pD	22.80			24.59		
DIC	152.25			157.31		
3-year OS rate for treatment vs reference						
σ	0.62	0.27	(0.17-1.24)	0.67	0.31	(0.14-1.40)
τ	9.02	65.04	(0.66-35.66)	49.29	1164.00	(0.51-48.58)
resdev	32.36	8.17	(18.39-50.07)	32.62	8.22	(18.52-50.51)
pD	28.02			28.65		
DIC	187.98			188.88		
5-year OS rate for treatment vs reference						
σ	0.80	0.46	(0.14-1.94)	0.60	0.42	(0.04-1.64)
τ	49.88	1159	(0.27-49.16)	5839.00	185600.00	(0.37-748.40)
resdev	22.54	6.73	(11.29-37.43)	22.57	6.519	(11.45-36.90)
pD	20.62			19.84		
DIC	132.23			131.49		

Table S13.

Posterior summaries from random effects consistency and inconsistency models for lesion (≤ 5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.49	0.13	(0.26-0.77)	0.29	0.14	(0.05-0.58)
τ	5.30	3.72	(1.70-14.33)	83.27	806.8	(2.94-391.70)
resdev	129.2	14.99	(101.40-160)	133.1	14.50	(105.70-162.80)
pD	84.95			78.28		
DIC	606.94			604.11		
3-year OS rate for treatment vs reference						
σ	0.50	0.09	(0.33-0.70)	0.47	0.096	(0.29-0.67)

τ	4.51	1.83	(2.08-9.02)	5.28	2.59	(2.24-11.80)
resdev	124	15.64	(95.16-156.40)	124.5	15.89	(95.35-157.50)
pD	93.89			93.37		
DIC	723.55			723.53		
5-year OS rate for treatment vs reference						
σ	0.44	0.10	(0.26-0.65)	0.44	0.1	(0.26-0.67)
τ	6.25	3.60	(2.38-14.90)	6.08	4.01	(2.25-14.87)
resdev	86.73	13.53	(62.35-115.40)	85.74	13.55	(61.39-114.40)
pD	67.86			68.84		
DIC	544.41			544.41		

sd: standard deviation;

CI: Credible Interval

σ: between-trial standard deviation

τ^2: between-trial variance

resdev: residual deviance

pD: effective number of parameters

DIC: deviance information criterion

Figure S1.

Results of the consistency test for closed loop at 1-year, 3-year, and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm.

i Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm

ii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm

iii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm

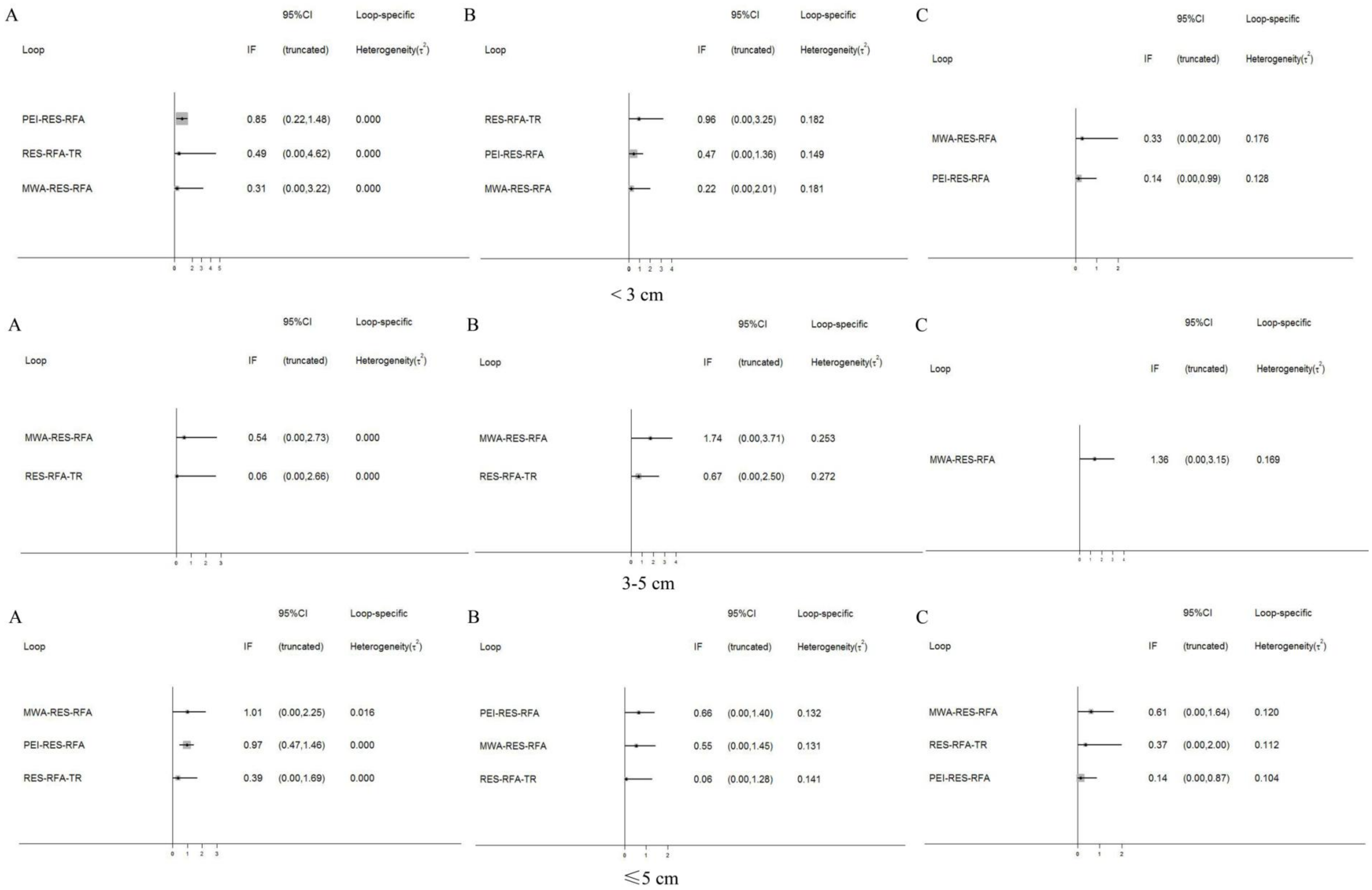

A
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.85 (0.22,1.48) 0.000
RES-RFA-TR 0.49 (0.00,4.62) 0.000
MWA-RES-RFA 0.31 (0.00,3.22) 0.000
B
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
RES-RFA-TR 0.96 (0.00,3.25) 0.182
PEI-RES-RFA 0.47 (0.00,1.36) 0.149
MWA-RES-RFA 0.22 (0.00,2.01) 0.181
C
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.33 (0.00,2.00) 0.176
PEI-RES-RFA 0.14 (0.00,0.99) 0.128
< 3 cm
A
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.54 (0.00,2.73) 0.000
RES-RFA-TR 0.06 (0.00,2.66) 0.000
B
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.74 (0.00,3.71) 0.253
RES-RFA-TR 0.67 (0.00,2.50) 0.272
C
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.36 (0.00,3.15) 0.169
3-5 cm
A
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.01 (0.00,2.25) 0.016
PEI-RES-RFA 0.97 (0.47,1.46) 0.000
RES-RFA-TR 0.39 (0.00,1.69) 0.000
B
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.66 (0.00,1.40) 0.132
MWA-RES-RFA 0.55 (0.00,1.45) 0.131
RES-RFA-TR 0.06 (0.00,1.28) 0.141
C
Loop IF 95%CI (truncated) Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.61 (0.00,1.64) 0.120
RES-RFA-TR 0.37 (0.00,2.00) 0.112
PEI-RES-RFA 0.14 (0.00,0.87) 0.104
≤5 cm

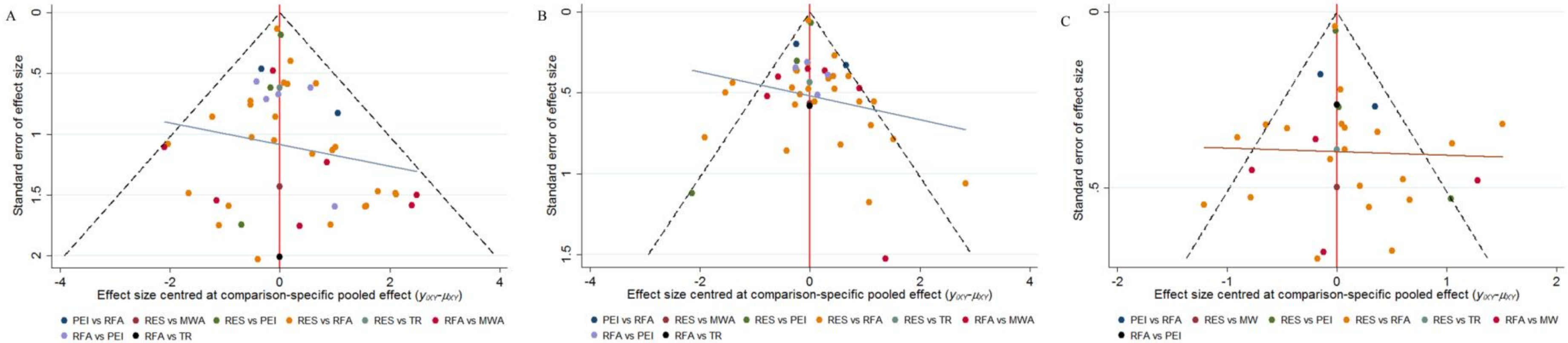
Figure S2.

Assessment of publication bias using funnel plot.

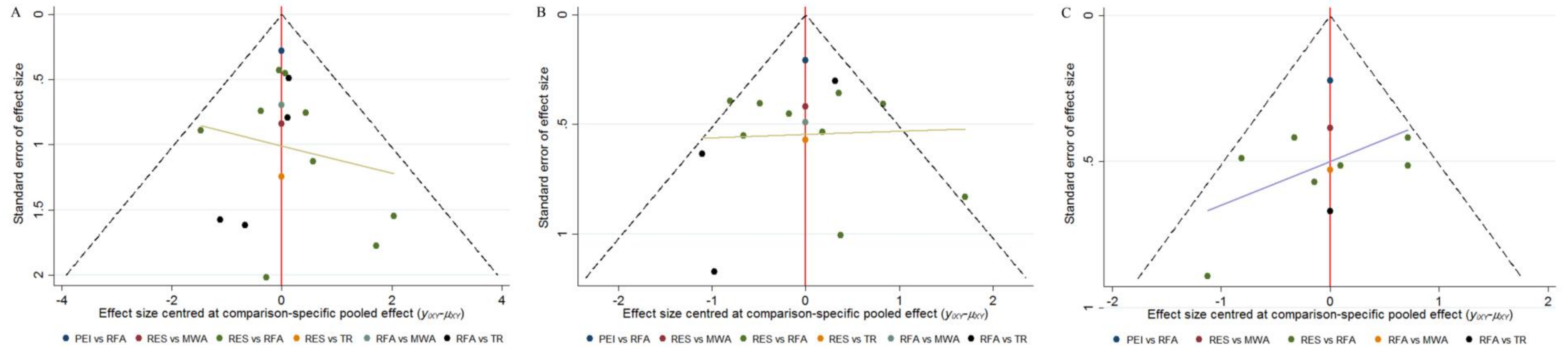
i Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm.

ii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm.

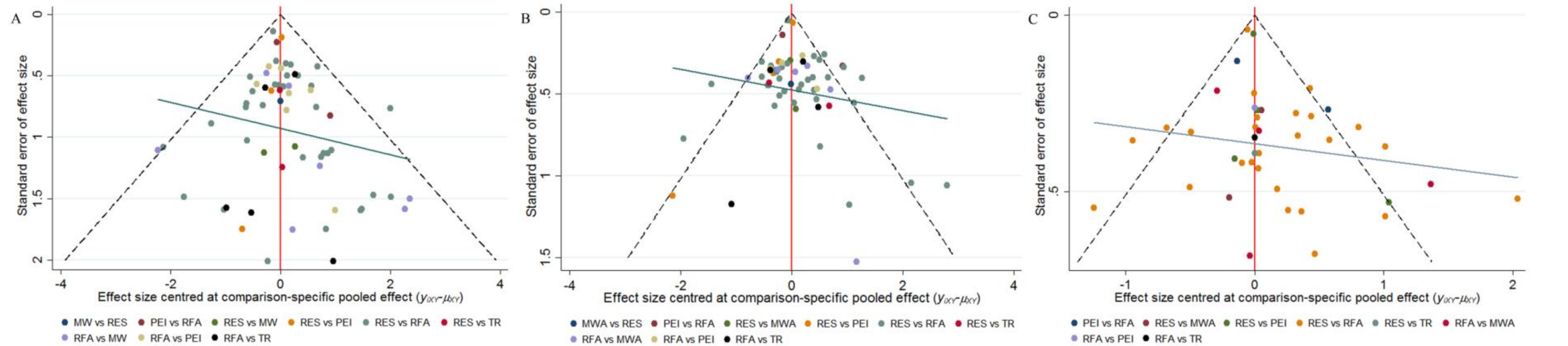
iii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm



i <3 cm



ii 3-5 cm



iii<5 cm

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8

METHODS

Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	11,12
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11,12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11,12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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Secondary Subject Heading:	Palliative care, Radiology and imaging, Surgery
Keywords:	resection, radiofrequency ablation, microwave ablation, transcatheter arterial chemoembolization, percutaneous ethanol injection, hepatocellular carcinoma

Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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Number of figures and tables: 7 figures and 15 tables

List of abbreviations in order of appearance: HCC: hepatocellular carcinoma; RES: resection; RFA: radiofrequency ablation; MWA: microwave ablation; TACE: transcatheter arterial chemoembolization; PEI: percutaneous ethanol injection; GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TR: TACE plus RFA; OS: overall survival; MCMC: Markov Chain Monte Carlo; CrI: credible interval; SUCRA: surface under the cumulative ranking curve LPS: lipopolysaccharide; TNFα: tumor necrosis factor α; IL: interleukin; TGFβ: transforming growth factor β.

Conflict of interest: The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement: No additional data are available.

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Author Contributions:

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3. Analyzed the data: Guo Tian, Shigui Yang, Jinqiu Yuan, Qiyu Zhao

4. Contributed reagents/materials/analysis tools: Qiyu Zhao, Fen Chen

5. Wrote the manuscript: Guo Tian, Shigui Yang, Tian'an Jiang

6. Critically revised and approved the final version of manuscript: Diane Threapleton, Hongcui Cao, Tian'an Jiang, Lanjuan Li

7. Study supervision: Hongcui Cao, Tian'an Jiang, Lanjuan Li

Abstract

Objective: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

Methods and analyses: We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

Results: We identified 74 studies, including 26944 patients. After adjustment for study design, and in the full sample of studies, the treatments were ranked in order of greatest to least benefit as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI. The ranks were similar for 1 and 3-year survival, with RES and TR being the highest ranking treatments. In both smaller (<3cm) and larger tumors (3-5cm), RES and TR were also the two highest ranking treatments. There was little evidence of inconsistency between direct and indirect evidence.

Conclusion: The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival. However, many of the between-treatment comparisons were not statistically significant and, for now, selection of strategies for treatment will depend patient and disease characteristics. Additionally, much of the evidence was provided by non randomised studies and knowledge gaps still exist.

More head-to-head comparisons between both RES and TR, or other approaches, will be necessary to confirm these findings.

Key words: resection; radiofrequency ablation; microwave ablation; transcatheter arterial chemoembolization; percutaneous ethanol injection; hepatocellular carcinoma.

Strengths and limitations of this study:

1. This is a network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

2. Strong and reliable methodological and statistical procedures were applied.

3. The individual or tumor characteristics within HCC articles would be a source of heterogeneity..

4. A major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival.

5. Other studies did not report the primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies.

Introduction

Cancer was the second leading cause of death in 2013, behind cardiovascular disease, and in 2013 more than 8 million people died from cancer globally [1-3]. Hepatocellular carcinoma (HCC) was the 6th most common cancer worldwide and the 3rd leading cause of cancer death, with 5-year overall survival rates under 12% [4 5].

Hepatic resection (RES) was the traditional choice for patients with HCC, without cirrhosis and with good remaining liver function [6]. Despite nearly 70% 5-year survival, recurrence rates after surgery were high [7]. Repeated hepatectomies to lengthen survival were not often appropriate owing to multiple-site tumor recurrence or patient background of liver cirrhosis [8 9]. Many locoregional therapies have been developed including ablative treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), or microwave ablation (MWA), and trans-arterial therapies such as transcatheter arterial chemoembolization (TACE) or transarterial chemotherapy infusion (TACI). Locoregional therapies were minimally invasive and therefore are cheaper and faster to recover, as compared to resection. Such approaches may be appropriate for patients with unresectable, small or multiple carcinomas or those with severe cirrhosis. However, there may be a greater risk of recurrence because of incomplete destruction of cancer cells at the treatment margin, as seen with RFA [10].

Selection of treatment strategy was determined by liver function, tumor stage and patient performance status [7], but much uncertainty still remains surrounding the comparative efficacy of different treatment approahces. A recent review of international guidelines for HCC found similarities but also some discrepancy in treatment allocation recommendations because of regional classification differences, secondary to a lack of solid or high-level evidence [11]. A recent review of therapies also revealed that there was no consensus on whether surgery or ablation was better for small tumors [7]. Some discrepancy in prevalence and treatment outcomes may be still in different regions because of local biology, available resources or expertise and access to care [11]. However, if we ever hope to achieve standardized and evidence-based therapy for HCC, the unanswered question surrounding relative treatment efficacy of RES compared to ablative locoregional therapies should be resolved.

Traditional meta-analysis is limited by existing head-to-head treatment comparisons within included studies. It is therefore not possible to gauge the relative benefit of two treatments that have never been directly compared in studies. Real-life treatment decisions are hindered by gaps in existing evidence, but network meta-analysis enables integration of direct and indirect comparisons to provide estimates for relative comparisons across many treatments [12]. In this study, we included the latest literature, and focused on the comparison of interventional and surgical treatments, including RES, RFA, MWA, and TACE plus RFA (TR), PEI. In order to investigate comparative effectiveness among RES and common locoregional ablative therapies, we performed a systematic review and network meta-analysis.

Search Strategy

We conducted a systematic review and report findings in accordance with PRISMA for Network Meta-Analyses (PRISMA-NMA) [13] (Additional file 1: Text S1). The following databases were searched: PubMed, Embase, Web of science and Scopus, up to May 2018, using these keywords: resection, surgery, hepatectomy, radiofrequency ablation, transarterial chemoembolization, microwave thermal ablation, ethanol injection, liver, cancer, tumor (Additional file 1: Text S2). No language restrictions were used. Bibliographies from other relevant review articles were cross-examined for potential missed studies. Disagreement was resolved by a third reviewer. Citations were downloaded into reference management software and duplicate citations were electronically or manually removed.

We systematically included the studies using the following criteria: 1) original data from prospective or retrospective cohort studies and randomized clinical trials (RCTs) in humans; 2) reporting at least two treatments, including resection or any local ablative therapy (RES, RFA, MWA, PEI, or TACE+RFA (TR)); 3) mean lesion size ≤ 5 cm; 4) evaluating overall survival rate not less than one year after first or recurrent treatments. Conference abstracts and case reports were excluded, as were older publications from studies with multiple publications.

Patients and public involvement

The patients or public were not involved in the study.

Data Extraction and Study Quality

Two investigators independently extracted and cross-checked the data from the eligible studies: author, year, study design, country, disease type, inclusion criteria, treatment style, study size, gender, age, tumor size, follow-up duration, treatment complications and survival outcomes. If in disagreement, a third reviewer adjudicated. The level of evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance [14], which was classified into four levels of high, moderate, low, and very low. The quality score was downgraded according to 5 domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias while scores were upgraded according to large effect, appropriate control for plausible confounding, and dose-response gradient.

Data Analysis

Network meta-analysis was used if a ring or open evidence loop was available to know the number of arms and the sample size of each intervention. When possible, pair-wise direct head-to-head comparisons were conducted to calculate the odds ratio (OR) of 1-, 3- and 5-year survival and their 95% confidence intervals (CI). Between-study heterogeneity was evaluated using the tau-squared statistic (τ^2) [15]. A node-splitting analysis was applied to check the consistency between direct evidence (existing real reported comparisons) and indirect evidence (estimated treatment comparisons) for their agreement on a specific node [16]. Bayesian network meta-analysis with Markov Chain Monte Carlo (MCMC), through a consistency model, was utilized to estimate the pooled ORs and its 95% credible interval (CrI) for the direct and indirect comparisons [16]. The inconsistency model was used to check for heterogeneity due to chance imbalance in the distribution of effect modifiers. Consistency in every closed loop was checked by the loop-specific approach in order to estimate whether treatment survival effects were disturbed by variance in the distribution of potential confounding factors among the studies. In order to compare and rank survival rates of different treatments, we examined all studies first and then separately assessed smaller (<3cm) and larger (3-5cm) tumors. Random-effect meta-regression models were used, with and without adjustment for study design (cohort or RCT) and subgroup analyses were also conducted for RCTs in order to examine treatment effectiveness. We appraised the ranking probabilities for all therapies for each intervention and the treatment hierarchy was ordered by the surface under the cumulative ranking curve (SUCRA) [17]. Sensitivity analysis was conducted to remove each study, in turn, and estimate the treatment effect in the remaining studies. Funnel plots were utilized to check the possible presence of publication bias or small-study bias [18]. In this study, we used Bayesian MCMC simulations by WinBUGS 1.4 and graphically presented the results using Stata 13.

Results

Study Characteristics

After screening, 74 relevant studies in 73 articles were identified, of which 20 were randomized controlled trials and 54 were cohort studies [19-92]. We excluded

136504 duplicate or non-relevant citations (Figure 1). The summary characteristics of these studies are shown in Additional file 1: Table S1. Overall, 32345 patients of mean age from 46 to 73.5 years, with approximately 29236 tumors, were assigned to receive RES, RFA, MWA, TR and PEI, and the mean follow-up ranged from 1.5 to 5.7 years. In addition, the numbers of connected studies to the lines (black) and sample size of each treatment (red) were shown in Figure 2 and 3, respectively.

Network Meta-Analysis Results

Ten possible treatment comparisons among the five interventions were examined in the included studies. Comparable survival estimates were made for each treatment (per 1000 patients) and the survival OR among each of the treatment comparisons, according to follow-up duration, are presented in Additional file 1: Table S2, along with estimation of the quality of evidence using GRADE criteria.

Across the range of treatment comparisons and follow-up durations, evidence was graded between low and high quality. Evidence was often graded as low quality owing to publication bias and graded as high quality owing to a larger number of participants in direct comparisons.

Survival probabilities (estimated using Meanrank) and ranks for the five treatments in patients with tumors <3cm, 3-5cm or ≤5cm (with and without adjustment for study design) are graphically displayed in Figures 2-5, and numerical details are given in Additional file 1: Table S3-S4. RES was consistently associated with greater survival (rank 1) compared to MWA, RFA, TR and PEI for the 5-year survival estimates. The ranks were similar for 1 and 3-year survival with RES or TR being ranked as 1 or 2 in most analyses. After adjustment for study design, and in the full sample of available studies (n=74), the treatments were ranked as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI (Table S4).

Efficacy comparisons from network meta-regression for all treatments are summarized in Table 1 and 2, according to follow-up duration and initial tumor size. Compared to RES, the 5-year survival in all studies (trials and observational studies) for all tumors ≤5cm, was 0.45 (95%CrI 0.23 to 0.82) for PEI, 0.59 (95%CrI 0.25 to 1.20) for TR, 0.55 (95%CrI 0.25 to 1.05) for MWA and 0.52 (95%CrI 0.29 to 0.88) for RFA (Table 2). When examining the comparisons across all treatments, the only significant difference for tumors <3cm was for 5-year survival, and a significantly worse survival was observed for PEI compared to RES 0.43 (95%CrI 0.17 to 0.89). For tumors between 3 and 5 cm, no significant differences were observed at 5-year survival, but significantly worse 3-year survival was observed with PEI, MWA and RFA compared to RES (Table 2). Despite smaller number of studies in analyses of only RCTs, the pairwise comparisons showed similar results. However, all relative rankings should be interpreted with caution because most network meta-regression comparisons did not suggest a statistically significant difference between treatments. Detailed results of each comparison for survival rates were shown in Additional file 1: Table S5-S10**.**

Loop-specific methods detected no inconsistency between the pairwise and network meta-analysis for most closed loops in the network (Additional file 1: Figure

S1). However, inconsistency was observed between direct and indirect comparisons for the following loops: lesions <3cm: RES-RFA-TR, PEI-RES-RFA, MWA-RES-RFA; lesions 3-5cm: MWA-RES-RFA, RES-RFA-TR; and lesions ≤5cm: RES-RFA-TR). In addition, tests for inconsistency were carried out (Additional file 1: Table S11-S13), which indicated a close relationship of between-trial heterogeneity and inconsistency between “direct” and “indirect” evidence.

Sensitivity Analysis and publication bias

No significant change was observed when any one study was deleted. Funnel plots indicated that the included studies in each group were distributed symmetrically around the vertical line (x=0), suggesting that no obvious evidence of publication bias or small-sample effect existed in this network (Additional file 1: Figure S2).

Discussion

There were many techniques for attaining a large ablated zone and complete necrosis of HCC and this comprehensive review addressed two of the more common treatments, namely resection and ablation. In this network meta-analysis, of the five examined therapies, the pooled data showed RES ranked best in full sample analysis with or without adjustment for study design. In both smaller (<3cm) and larger tumors (3-5cm) RES remained the highest ranking treatment. However, most of the individual treatment comparisons were not statistically significant and thus, RES may not be superior to all other therapies. Our evidence indicated locoregional therapies and particularily RES or TR (TACE+RFA) were associated with longer survival.

Our observation of better survival outcomes with TR may be through the advantage of dual mechanisms. With TR, TACE induced hypoxic injury on cancer cells through occlusion of blood vessels and was followed by local ablation. This combination therapy may result in a larger ablated zone [93], reducing the possibility of micrometastasis and recurrence, and thus, resulting in better survival outcomes than RFA alone.

While being more invasive, and despite risk of complications, RES was associated with better survival outcomes after 1 year, 3 years and 5 years. This may be due to removal of larger sections of liver than can be targeted with locoregional therapies, thus removing a larger area of potentially cancerous cells. Additionally, rat models indicated that the liver has the potential to quickly restore its original size after partial hepatectomy. This may be mediated via interactions of lipopolysaccharide (LPS), tumor necrosis factor (TNF)α, interleukin (IL)-6, and transforming growth factor β (TGFβ) [94]. However, evidence from rat models and human studies indicated that resection success was associated with resection size and regeneration was stunted with larger resections [95-97]. The safe limit for remnant liver volume in normal liver was approximately 30% of total liver volume, but this was estimated to rise to 40-50% in those with liver disease [95 98]. Liver resection was recognised as the most efficient treatment for HCC but was only applicable for less than 30% of all patients. However, developments in preoperative imaging tachniques, laproscopic surgery and newly developing combinations with chemotherapy may extend its application to more advanced tumors [98]. Furthermore, the consistent associations observed with all studies and only in RCTs indicated that patient selection bias in the observational studies does not wholly explain the better survival outcomes with RES.

Overall, we found PEI was associated with shorter survival than the other four therapies, a finding which is supported in previous studies [20 29]. One study reported RFA was superior to PEI in achieving short- and long-term survival outcomes, although PEI and RFA showed similar 5-year survival in lesions <3 cm [51]. The possible reason why PEI is less effective than RFA may be because lesions often have a thick capsule and therefore ethanol may not distribute through tissues.

There are several limitations in this study. Firstly, a major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival. Secondly, this study included both RCTs and observational studies, in which study designs and type of data collection may not be comparable. However, findings were consistent among both study designs. Thirdly, all included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies. Fourthly, for many individual comparisons, there were either no direct comparisons or comparisons from only a small number of studies. The lack of evidence may increase the risk of bias, which could enlarge or undervalue effect size, and may explain the small inconsistency seen between direct and estimated comparisons. Thus, we should be cautious in interpreting treatment rankings for the different survival times and for different size lesions. While adverse events from treatments may differ (not evaluated in detail in this review), by examining overall survival outcomes in our review, we have taken account of both long-term potential benefits and harms from treatments. The focus of these findings should therefore be on the overall observation that RES or TR may be superior in terms of survival, rather than focusing on specific OR values for individual treatment comparions.

In conclusion, the findings of the current bayesian network meta-analysis indicate that RES or TR may be among the most effective therapeutic approaches for HCC for 5-year survival in both smaller (< 3cm) and larger (3-5cm) lesions. However, evidence was of variable quality, and the majority of evidence came from non randomised studies, which are prone to selection bias and knowledge gaps still exist. For not, at the individual level, selection of strategies should depend on patient and clinical characteristics. To facilitate generation of evidence-based recommendations for HCC therpy, and to standardize treatment approaches, further head-to-head comparisons, especially of resection and ablative therapies, are required from high-quality RCTs, with long follow-up for survival outcomes.

Conflict of interests

The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement

No additional data are available.

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File legends:

Figure 1 Flow chart of search.

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according

to lesion size in RCTs

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Table 1 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in randomized controlled trials.

〈3cm for 1-year survival

PEI				
1.17 (0.11-4.66)	TR			
0.08 (0-0.38)	**0.15 (0-0.80)**	MWA		
0.67 (0.28-1.35)	1.25 (0.16-4.64)	**173.30 (1.90-537.40)**	RFA	
0.64(0.18-1.61)	1.08 (0.15-3.78)	**152.70 (1.44-505.80)**	0.97 (0.42-1.98)	RES

〈3cm for 3-year survival

PEI				
1.02 (0.14-3.56)	TR			
NA	NA	MWA		
0.79 (0.45-1.39)	1.54 (0.25-13.43)	NA	RFA	
0.58 (0.29-1.16)	1.17 (0.16-4.17)	NA	0.75 (0.41-1.31)	RES

〈3cm for 5-year survival

PEI				
3.93 (0.03-19.61)	TR			
NA	NA	MWA		
0.94 (0.08-3.97)	2.87 (0.04-13.43)	NA	RFA	
0.50 (0.04-2.04)	0.84 (0.03-4.18)	NA	0.72 (0.10-2.47)	RES

3-5cm for 1-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.40 (0.64-11.93)	NA	RFA	
NA	1.00 (0-5.00)	NA	0.25 (0-1.47)	RES

3-5cm for 3-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.98 (0.71-15.22)	NA	RFA	
NA	1.14 (0-6.20)	NA	0.24 (0-1.25)	RES

3-5cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	7.64 (0.14-42.49)	NA	RFA	
NA	12.87 (0.02-44.43)	NA	1.05 (0.03-5.33)	RES

≤5cm for 1-year survival

PEI				
0.29 (0.09-0.73)	TR			
0.27 (0.05-0.84)	1.09 (0.16-3.50)	MWA		
0.65 (0.33-1.13)	**2.69 (1.02-6.04)**	3.84 (0.81-11.60)	RFA	
0.37 (0.13-0.82)	1.50 (0.48-3.67)	2.01 (0.47-5.70)	0.57 (0.27-1.08)	RES

≤5cm for 3-year survival

PEI				
0.64 (0.19-1.67)	TR			
1.05 (0.12-4.56)	1.86 (0.21-7.59)	MWA		
0.86 (0.39-1.79)	1.56 (0.66-3.25)	1.77 (0.22-6.24)	RFA	
0.55 (0.19-1.44)	0.98 (0.35-2.41)	1.00 (0.16-3.30)	0.65 (0.31-1.29)	RES

≤5cm for 5-year survival

PEI				
0.53 (0.06-1.90)	TR			
NA	NA	MWA		
0.74 (0.16-2.00)	2.29 (0.41-7.61)	NA	RFA	
0.41 (0.11-1.02)	1.35 (0.23-4.69)	NA	0.66 (0.20-1.62)	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

Table 2 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in all studies

〈3cm for 1-year survival

PEI				
0.69 (0.14-2.13)	TR			
0.49 (0.18-1.10)	1.08 (0.21-7.87)	MWA		
0.68 (0.38-1.09)	1.48 (0.34-4.23)	1.59 (0.69-3.17)	RFA	
0.63 (0.22-1.44)	1.30 (0.28-3.88)	1.49(0.44-3.85)	0.94 (0.39-1.91)	RES

〈3cm for 3-year survival

PEI				
0.90 (0.29-2.17)	TR			
1.01 (0.47-1.95)	1.38 (0.42-3.40)	MWA		
0.96(0.59-1.50)	1.31 (0.47-2.92)	1.02 (0.57-1.70)	RFA	
0.68 (0.30-1.39)	0.90 (0.31-2.10)	0.73 (0.30-1.55)	0.72 (0.37-1.30)	RES

〈3cm for 5-year survival

PEI				
1.07 (0.31-2.72)	TR			
0.86 (0.39-1.65)	1.03 (0.28-2.73)	MWA		
0.82 (0.48-1.29)	0.99 (0.32-2.39)	1.04 (0.50-1.77)	RFA	
0.43 (0.17-0.89)	**0.49 (0.16-0.18)**	0.55 (0.19-1.25)	0.54 (0.24-1.05)	RES

3-5cm for 1-year survival

PEI				
0.20 (0.05-0.54)	TR			
0.55 (0.09-1.76)	3.39 (0.58-10.44)	MWA		
0.49 (0.18-1.12)	**2.99 (1.14-6.58)**	1.29 (0.32-3.60)	RFA	
0.06 (0-0.31)	0.36 (0.01-2.08)	0.15 (0-1.00)	**0.12 (0-0.63)**	RES

3-5cm for 3-year survival

PEI				
0.28 (0.04-0.96)	TR			
0.61 (0.08-2.26)	2.62 (0.61-7.90)	MWA		
0.55 (0.12-1.69)	2.38 (0.93-5.38)	1.15 (0.39-2.65)	RFA	
0.06 (0-0.28)	0.26 (0.01-1.10)	**0.12 (0.01-0.53)**	**0.11 (0.01-0.40)**	RES

3-5cm for 5-year survival

PEI				
5.77 (0.01-2.84)	TR			
4.15 (0.04-5.18)	11.97 (0.19-46.76)	MWA		
0.86 (0.06-2.68)	6.16 (0.27-25.58)	1.26 (0.19-4.04)	RFA	
3.02 (0.01-2.40)	14.31 (0.04-21.06)	1.24 (0.02-4.46)	0.69 (0.04-3.16)	RES

≤5cm for 1-year survival

PEI				
0.34 (0.11-0.63)	TR			
0.81 (0.38-1.51)	2.69 (0.99-6.00)	MWA		
0.77 (0.51-1.10)	**2.55 (1.20-4.85)**	1.04 (0.55-1.76)	RFA	
0.52 (0.24-0.96)	1.72 (0.66-3.70)	0.70 (0.29-1.39)	0.68 (0.35-1.17)	RES

≤5cm for 3-year survival

PEI				
0.64 (0.32-1.16)	TR			
0.98 (0.55-1.65)	1.65 (0.80-3.03)	MWA		
0.94 (0.64-1.34)	1.57 (0.89-2.57)	0.99 (0.64-1.47)	RFA	
0.59 (0.30-1.04)	0.97 (0.48-1.79)	0.62 (0.32-1.09)	0.63 (0.37-1.01)	RES

≤5cm for 5-year survival

PEI				
0.84 (0.35-1.74)	TR			
0.87(0.46-1.51)	1.16 (0.46-2.46)	MWA		
0.87 (0.57-1.26)	1.16 (0.54-2.21)	1.06 (0.64-1.61)	RFA	
0.45 (0.23-0.82)	0.59 (0.25-1.20)	0.55 (0.25-1.05)	**0.52 (0.29-0.88)**	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

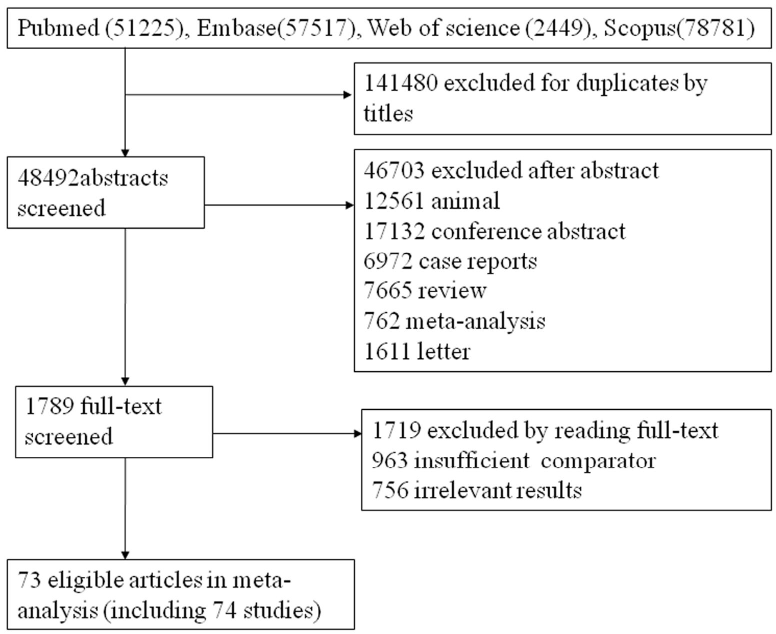

Figure 1 Flow chart of search.

254x190mm (300 x 300 DPI)

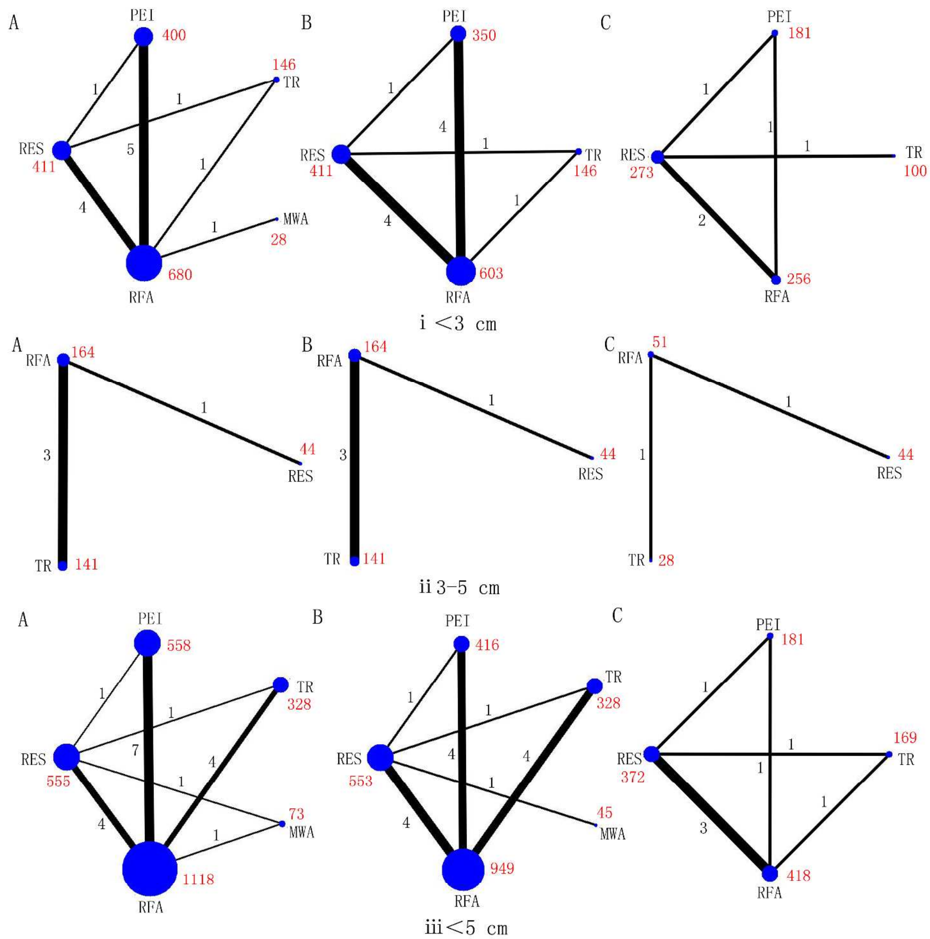

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

500x500mm (300 x 300 DPI)

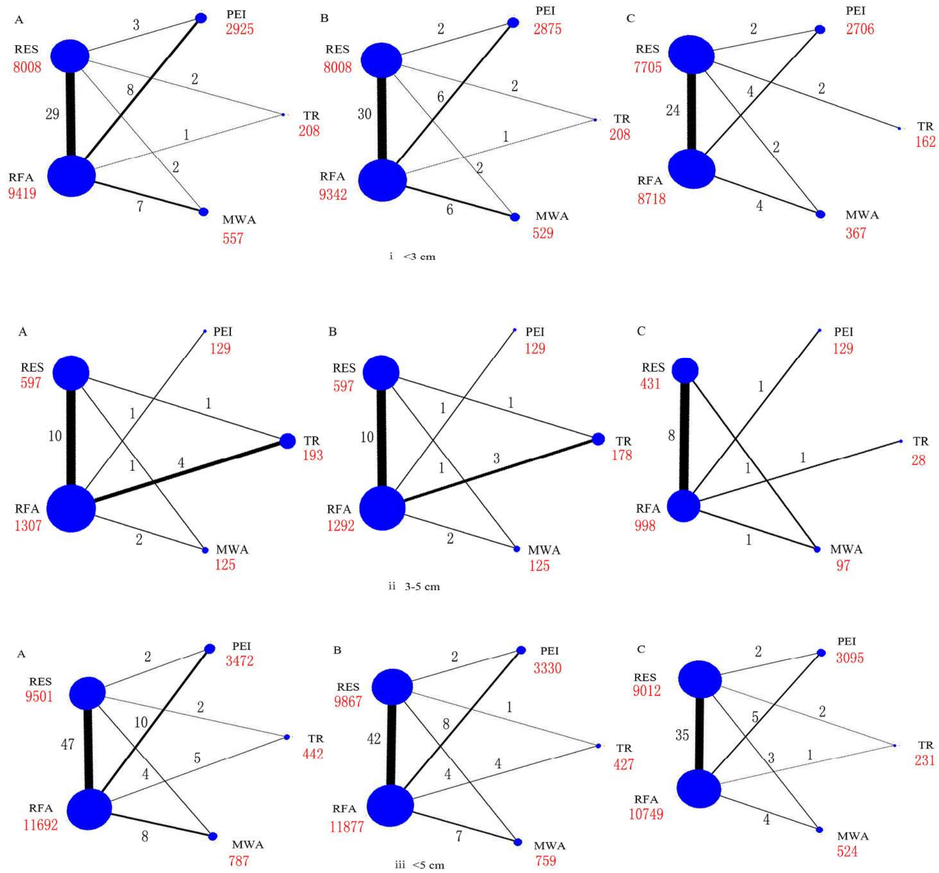

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

227x227mm (300 x 300 DPI)

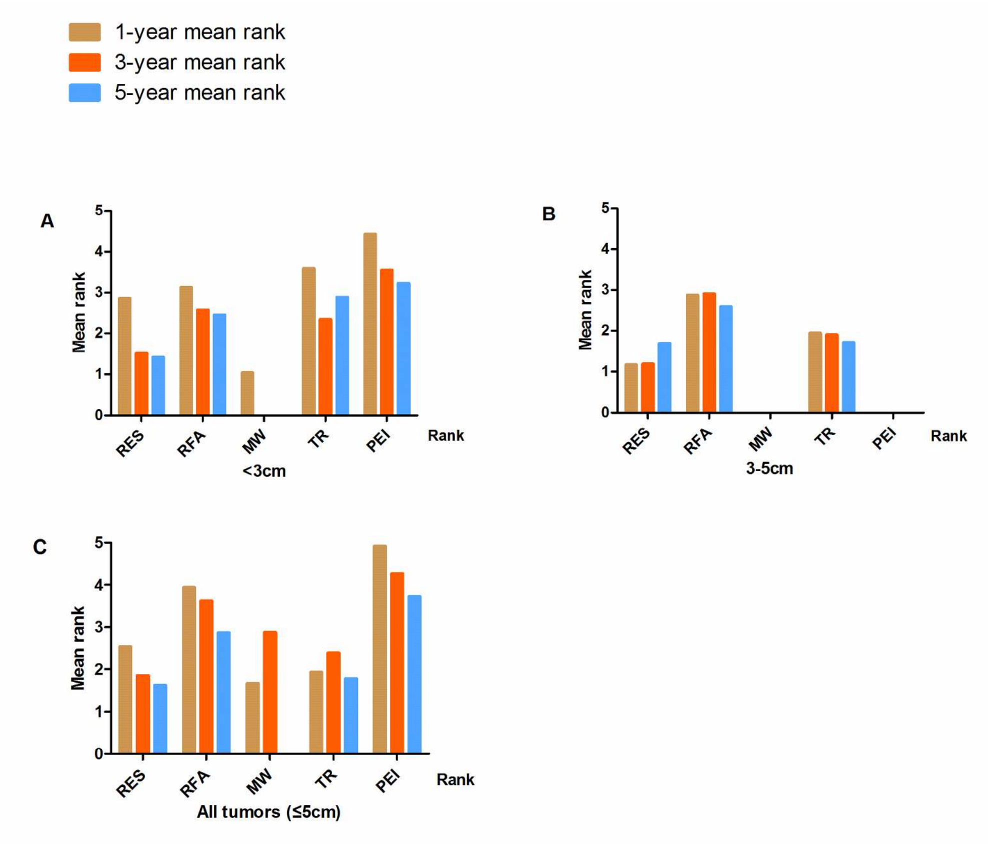

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

193x165mm (300 x 300 DPI)

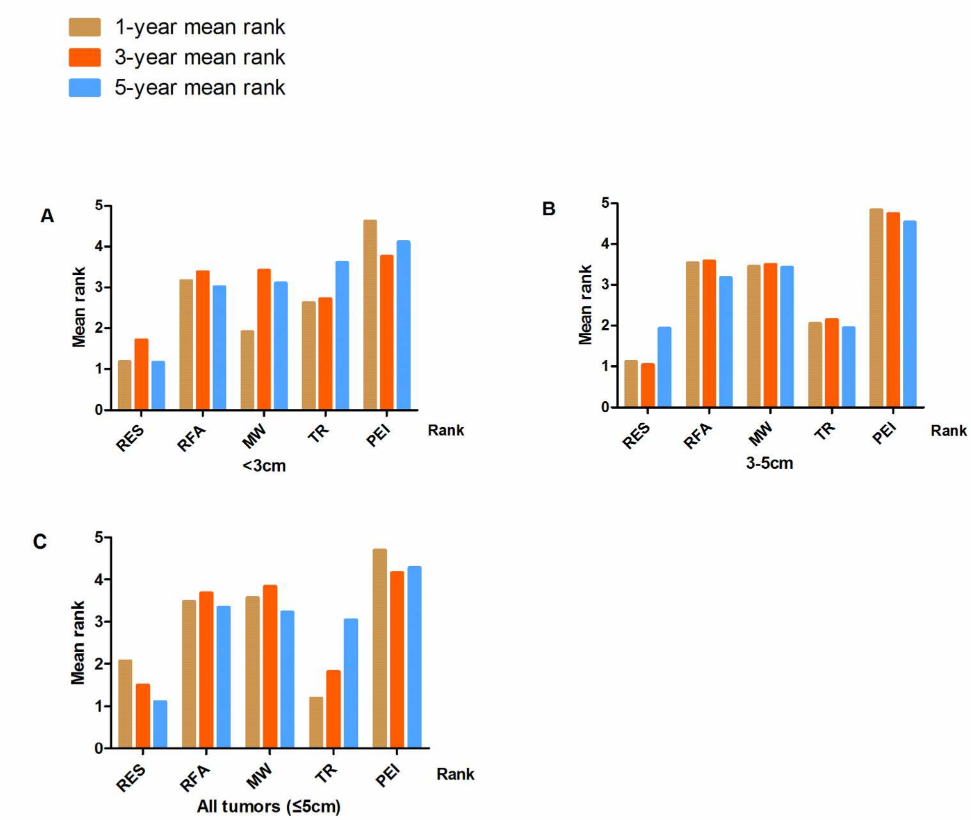

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

193x165mm (300 x 300 DPI)

Text S1.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and*	11,12

		• *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the	17

	authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Text S2.

Search strategy:

Pubmed (1950-present)

1. ("TACE" OR "transarterial chemoembolization")
2. ("RFA" OR "radiofrequency ablation" OR "RF ablation" OR "radiofrequency thermal ablation" OR "RTA")
3. (PEI OR "ethanol injection" OR "ethanol ablation" OR "alcohol ablation")
4. ("microwave ablation" OR "microwave thermal ablation" OR MWA)
5. (liver OR hepato*)
6. (neoplas* OR cancer OR tumor OR tumour OR carcinoma OR oncolog*)
7. 1 OR 2 OR 3 OR 4
8. 5 AND 6 AND 7
9. "Ablation Techniques"[Mesh]
10. "Embolization"[Mesh]
11. "Liver Neoplasms"[Mesh]
12. 9 OR 10
13. 12 AND 11
14. 8 OR 13
15. (resection OR surgery OR hepatectomy)
16. (ablation OR injection OR embolization)
17. 5 AND 6 AND 15 AND 16
18. "Hepatectomy"[Mesh]
19. 12 AND 18 AND 11
20. 17 OR 19

21. 14 OR 20

Embase(1980-present)

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2. ' transarterial chemoembolization':ab,ti
3. 1 OR 2
4. 'rfa':ab,ti
5. 'radiofrequency ablation':ab,ti
6. 'rf ablation':ab,ti
7. 'radiofrequency thermal ablation':ab,ti
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Scoups

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2. TITLE-ABS-KEY (“transarterial chemoembolization”)
3. 1 OR 2
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Web of science

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2. TS=(embolization)
3. 1 OR 2

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Table S1.
Summary of the studies included in the network meta-analysis.

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2002 [19]	Prospective cohort	China	HCC	0.3-2	RFA	15(15)	13/2	61.8 (38-78)	4.1 (2.4-6.0)	NA	0.80(1y)	0.80(1y)	NA
					TR	15(15)	12/3	57.8 (39-72)	4.6 (2.3-7.1)	NA	1.00(1y)	1.00 (1y)	NA
Lencioni 2003 [20]	RCT	Italy	HCC	1.9 ±0.8	RFA	52(69)	36/16	67 ±6 (52-78)	2.8 ±0.6	1.00(1y)	NA	1.00(1y)	15 pain and 10 fever
					PEI	50(73)	30/20	69 ±7.4 (40-82)	2.8 ±0.8	0.96(1y)	NA	0.96(1y)	13 pain and 5 fever
Lin 2004 [21]	RCT	China	HCC	2 ±0.9	RFA	52(69)	35/17	62 ±11	2.9 ±0.8	0.76(3y)	NA	0.35(3y)	1 transient pleural effusion

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					PEI	52(67)	34/18	59±10	2.8±0.8	0.66(3y)	NA	0.17(3y)	1 pain
Vivarelli 2004 [22]	Retrospective cohort	Italy	HCC	2.4	RES	79(92)	57/22	65.2±8.2 (43-81)	≤3/3.1-5 (21/58)	0.81(3y)	0.59(3y)	0.65(3y)	NA
					RFA	79(112)	67/12	67.8±8.7 (41-88)	≤3/3.1-5 (22/57)	0.50(3y)	0.25(3y)	0.33(3y)	NA
Cho 2005 [23]	Retrospective cohort	Korea	HCC	0.1-3	RES	61	48/13	57	3.4±1.0	NA	0.77(3y)	0.77(3y)	2 bleeding, 1 intraabdominal abscess, 1 wound infection
					RFA	99	76/23	58	3.1±0.8	NA	0.80(3y)	0.80(3y)	1 chest wall metastasis, 1 cholecystitis, 1 iatrogenic burn, 1 ileus, 1 hepatic infarction
Huang 2005 [25]	RCT	China	HCC	1-4.9	RES	38(42)	27/11	59±11.4	≤2/2.1-3 (24/14)	0.82	NA	0.82	NA
					PEI	38(46)	19/19	63±10.9	≤2/2.1-3 (21/17)	0.45	NA	0.45	NA
Hong 2005 [24]	Retrospective cohort	Korea	HCC	2.9(0.4-4.6)	RES	93	69/24	49.2±9.9	2.5±0.8	0.84(3y)	NA	0.84(3y)	NA
					RFA	55	41/14	59.1±9.6	2.4±0.6	0.73(3y)	NA	0.73(3y)	NA
Lin 2005 [26]	RCT	China	HCC	2.3±1	RFA	62(78)	40/22	61±10	2.5±1	0.74(3y)	NA	0.74(3y)	2 haemothorax, 1 gastric bleeding and perforation
					PEI	62(76)	39/23	60±8	2.3±0.8	0.60(3y)	NA	0.60(3y)	1 pain
Lu 2005 [27]	Retrospective cohort	China	HCC	2.1±1.1	RFA	53(72)	43/10	54.5±11.7 (24-74)	2.6±1.2 (1.0-6.1)	0.38(3y)	NA	0.38(3y)	2 skin burn, 1 puncture wound infection
					MWA	49(98)	44/5	50.1±13.7 (24-74)	2.5±1.2 (0.9-7.2)	0.51(3y)	NA	0.51(3y)	2 puncture wounds, 2 subcapsular hematoma

Study Year	Design style	Countr,	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Montorsi 2005 [28]	Prospective cohort	Italy	HCC	2.1	RES	40	33/7	67 ±9	<5cm	NA	NA	0.73(3y)	NA
					RFA	58	43/15	67 ±6		NA	NA	0.60(3y)	NA
Shiina 2005 [29]	RCT	Japan	HCC	3.1(0.6-4.3)	RFA	118(184)	79/39	≤65/>65 (44/74)	≤2/>2 (45/73)	NA	NA	0.61(3y)	1 transient jaundice, 1 skin burn, 1 hepatic infarction, 3 neoplastic seeding
					PEI	114(188)	87/27	≤65/>65 (41/73)	≤2/>2 (57/57)	NA	NA	0.45(3y)	1 abscess2 neoplastic seeding
Chen 2006 [30]	RCT	China	HCC	2.4 ±1	RES	90	75/15	49.4 ±10.9	≤3/3.1-5 (42/48)	0.53	NA	0.53	2 liver failure, 2 gastrointestinal bleeding, 27 ascites
					RFA	71	56/15	51.9 ±11.2	≤3/3.1-5 (37/34)	0.58	NA	0.58	3 skin burn
Lu 2006 [31]	RCT	China	Early HCC	1.8	RES	54(56)	37/17	49 ±14	3.2 ±1.0	NA	NA	0.86 (3y)	3 wound infection, 1 gastrointestinal bleeding
					RFA	51(57)	42/9	55 ±13	2.7 ±1.0	NA	NA	0.87 (3y)	1 peritoneal bleeding, 1 neoplastic seeding
Cho 2007 [32]	Retrospective cohort	Korea	HCC	5.7	RES	130(145)	103/27	56.3 ±8.8	≤2/2.1-3 (43/87)	0.66	NA	0.66	NA
					PEI	249(275)	181/68	57.7 ±9.7	≤2/2.1-3 (169/80)	0.49	NA	0.49	NA
Gao 2007 [33]	Retrospective cohort	China	HCC	4.6	RES	34(37)	28/6	51.5 (38-67)	2.58 ±0.41	0.76	NA	0.76	12 fever, 5 ascites
					RFA	53(84)	41/12	57.1 (31-81)	2.45 ±0.37	0.62	NA	0.62	2 bleeding, 1 fistula, 1 wound infection, 6 fever, 9 ascites
Lupo 2007 [34]	Retrospective cohort	Italy	HCC	2.6	RES	42	33/9	67(28-80)	4.0(3-5)	NA	0.43	0.43	2 urine infection, 1 bilioma, 1 pleural effusion, 1 renal failure, 1 intra-abdominal bleeding

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	60	47/13	68(42-85)	3.65(3-5)	NA	0.32	0.32	2 liver failure, 1 hepatic abscess, 2 pleural effusion, 1 cutaneous metastasis
Zhou 2007 [35]	Retrospective cohort	China	HCC	0.5-5.9	RES	40(42)	35/5	53±13	≤2/2.1-5 (7/33)	NA	NA	0.75	NA
					RFA	47(54)	37/10	57±14	≤2/2.1-5 (8/39)	NA	NA	0.19	NA
Abu-Hilal 2008 [36]	Retrospective cohort	Italy and China	Early HCC	3.6	RES	34	26/8	67	3.8(1.3-5)	NA	0.56	0.56	3 hepatic failure
					RFA	34	27/7	65	3(2-5)	NA	0.56	0.56	1 artero-portal fistula
Brunello 2008 [37]	RCT	Italy	Early HCC	2.2	RFA	70(89)	49/20	70.3±8.1	1.27±0.54	0.60(3y)	NA	0.60(3y)	1 haemoperitoneum 1 right haemothorax
					PEI	69(88)	43/27	69.0±7.7	1.27±0.57	0.58(3y)	NA	0.58(3y)	1 haemoperitoneum 1 death
Guglielmi 2008 [38]	Retrospective cohort	Italy	HCC	2.3	RES	91(113)	73/18	≤65/>65 (47/44)	≤3/3.1-6 (31/60)	0.55	0.43	0.48	33 postoperative complications
					RFA	109(153)	88/21	≤65/>65 (38/71)	≤3/3.1-6 (32/77)	0.28	0.14	0.20	11 postoperative complications
Hiraoka 2008 [39]	Retrospective cohort	Japan	HCC	2.5	RES	59	44/15	62.4±10.6	2.27±0.55	0.59	NA	0.59	1 death, 2 abscess
					RFA	105	76/29	69.4±9.1	1.98±0.52	0.59	NA	0.59	1 biloma, 2 dermatitis
Bu 2009 [45]	Retrospective cohort	China	HCC	2.9(0.5-6)	RES	42(46)	36/6	53.93±10.74	≤3/3.1-5 (14/28)	0.57	0.46	0.50	1 postoperative hemorrhage, 3 pleural effusions, 2 subdiaphragmatic effusion

Study Year	Design style	Countr	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					RFA	46(54)	40/6	55.89±7.37	≤3/3.1-5 (20/26)	0.50	0.31	0.37	4 pleural effusions, 1 postoperative hemorrhage, 1 skin burn
Ohmoto 2009 [40]	Retrospective cohort	Japan	HCC	2.8±2	RFA	34(37)	25/9	67 (44-78)	1.6 (0.7-2.0)	0.71	NA	0.71	2 pain, 4 fever, 1 bile duct injury, 1 pleural effusion, 1 skin burns, 1 vagovagal reflex
					MWA	49(56)	41/8	64 (38-75)	1.7 (0.8-2.0)	0.37	NA	0.37	11 pain, 17 fever, 9 bile duct injury, 8 pleural effusion, 5 ascites, 4 skin burns, 2 vagovagal reflex, 2 abscess, 2 intraperitoneal bleeding, 1 hepatic infarction, 1 portal thrombus, 1 biliary peritonitis
Sakaguchi 2009 [41]	Retrospective cohort	Japan	HCC	0.1-5	Laparoscopic /thoracoscopic RFA	249	169/80	65.6±8.9	2.48±0.89	0.57	NA	0.57	1 frequent premature ventricular contractions, 1 liver decompensation
					Laparoscopic /thoracoscopic MWA	142	107/35	64.9±7.8	2.28±0.74	0.63	NA	0.63	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Santambrogio 2009 [42]	Prospective cohort	Italy	HCC	3.2	RES	78	55/23	68±8	2.87±1.21	0.54	NA	0.54	15 extra-hepatic complications

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					Laparoscopic RFA	74	59/15	68±7	2.63±1.07	0.41	NA	0.41	14 extra-hepatic complications
Shibata 2009 [43]	RCT	Japan	HCC	2.5±1.2	RFA	43(44)	33/10	69.8±8 (44-87)	1.6±0.5 (0.8-2.6)	0.84(3y)	NA	0.84(3y)	1 pseudoaneurysm
					TR	46(49)	31/15	67.2±8.9 (45-83)	1.7±0.6 (0.9-3.0)	0.85(3y)	NA	0.85(3y)	1 hepatic infarction
Ueno 2009 [44]	Retrospective cohort	Japan	HCC	3(0.3-7.9)	RES	123(136)	82/41	67(28-85)	2.7±0.1	0.81	0.72	0.80	NA
					RFA	155(209)	100/55	66(40-79)	2.0±0.1	0.38	0.78	0.63	NA
Guo 2010 [46]	Retrospective cohort	China	HCC	2.5	RES	73(155)	57/16	50.0 (17.0-68.0)	≤3/3.1-5 (30/43)	0.27	0.47	0.44	1 postoperative hemorrhage, 5 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	86(211)	63/23	52.5 (26.0-80.0)	≤3/3.1-5 (42/44)	0.33	0.16	0.21	1 postoperative hemorrhage, 1 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Huang 2010 [47]	RCT	China	HCC	3.87	RES	115(144)	85/30	55.91±12.68	≤3/3.1-5 (45/44)	0.82	0.73	0.76	1 hepatic failure, 13 ascites, 5 effusion, 9 bile leakage, 2 postoperative bleeding, 2 gastrointestinal bleeding
					RFA	115(147)	79/36	56.57±14.30	≤3/3.1-5 (57/27)	0.61	0.52	0.55	1 gastric perforation, 2 hemorrhage, 1 malignant seeding, 1 hepatic infarction
Kagawa 2010 [48]	Retrospective cohort	Japan	Early HCC	4.2	RES	55(69)	40/15	66.1±8.4	≤2/2.1-5 (9/46)	0.42	NA	0.42	2 deaths, 1 liver failure, 1 pleural effusion, 1 pneumonia, 2 biliary leakage

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					TR	62(79)	39/23	67.5±8.4	≤2/2.1-5 (19/43)	0.29	NA	0.29	1 duodenal perforation, 1 hemothorax
Morimoto 2010 [49]	RCT	Japan	HCC	2.7	RFA	18(25)	12/6	73 (48-84)	3.7±0.6	NA	0.78(3y)	0.78(3y)	5 pain, 2 pleural effusion
					TR	19(21)	15/4	70 (57-78)	3.6±0.7	NA	0.95(3y)	0.95(3y)	1 pain, 1 pleural effusion
Azab 2011 [50]	RCT	Egypt	HCC	1.5	RFA	30(33)	75/15	46-77	<5cm	NA	NA	0.90	5 superficial burn, 17 transient pain, 3 portal vein thrombosis, 7 fever, 1 ascites
					PEI	30(32)				NA	NA	0.83	2 portal vein thrombosis, 3 fever, 3 ascites
Giorgio 2011 [51]	RCT	Italy	HCC	1.8	RFA	142	105/37	70±2 (68-74)	2.34±0.45 (1.1-3)	0.70	NA	0.70	1 major complication
					PEI	143	102/41	72±6 (68-79)	2.27±0.48 (1.3-2.9)	0.68	NA	0.68	3 major complication
Hung 2011 [52]	Retrospective cohort	China	Early HCC	3.5±2	RES	229	184/45	60.07±12.56	2.88±1.06	0.77	NA	0.77	NA
					RFA	190	121/69	67.42±11.45	2.37±0.92	0.67	NA	0.67	NA
Nishikawa 2011 [53]	Retrospective cohort	Japan	HCC	3.3	RES	69	50/19	67.4±9.7	2.68±0.49	0.74	NA	0.74	2 bile leakage, 2 ascites, 1 acute respiratory distress syndrome, 1 gastrointestinal bleeding
					RFA	162	95/67	68.4±8.7	1.99±0.62	0.63	NA	0.63	1 biloma, 1 ascites, 1 intra-abdominal bleeding
Yun 2011 [54]	Retrospect	Korea	HCC	3.5(0.1-9.	RES	215	171/44	51.7±9.7	2.1±0.5	0.94	NA	0.94	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
	ive cohort			1)	RFA	255	197/58	57.0 ±9.9	2.1 ±0.5	0.87	NA	0.87	NA
Zhang 2011 [55]	Retrospective cohort	China	HCC	0.5-3.5	RES	103(117)	78/25	56.4 ±15.2	<5cm	NA	NA	0.35(3y)	12 wound infection, 5 postoperative hemorrhage, 2 hepatic failure, 15 pleural effusions, 6 pleural effusions
					RFA	85(106)	62/23	58.5 ±12.9	<5cm	NA	NA	0.39(3y)	2 gallbladder cardiac reflex, 4 postoperative hemorrhage, 3 pleural effusions
Feng 2012 [57]	RCT	China	HCC	3	RES	84(116)	75/9	47 (18-76)	2.6 ±0.8	0.62(3y)	NA	0.62(3y)	7 pleural effusion, 3 pneumonia, 1 effusion plus infection, 3 wound infection or dehiscence, 1 biliary fistula, 2 abdominal bleeding, 1 pneumothorax or hemothorax
					RFA	84(120)	79/5	51 (24-83)	2.4 ±0.6	0.55(3y)	NA	0.55(3y)	5 pleural effusion, 1 liver abscess, 2 abdominal bleeding
Peng 2012 [58]	Retrospective cohort	China	Recurrent HCC	4.9	RES	74	65/9	51.5 ±12.1 (24-75)	1.1 ±0.5 (0.8-2.0)	0.62	NA	0.62	1 liver failure, 2 gastrointestinal bleeding, 1 peritoneal bleeding, 1 intestinal obstruction, 1 spontaneous bacterial peritonitis, 1 persistent jaundice, 31 ascites

Study Year	Design style	Countr ,	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					RFA	71	63/8	53.1±12.1 (28-74)	1.2±0.6 (0.9-2.0)	0.72	NA	0.72	1 gastrointestinal bleeding, 1 persistent jaundice, 12 ascites
Peng 2012 [59]	RCT	China	Recurrent HCC	3.3±1.8	RFA	70(76)	55/15	55.1±9.5 (22-75)	≤3/3.1-5 (46/24)	NA	0.17	0.36	1 persistent jaundice, 1 ascites, 22 fever, 45 pain, 4 vomiting
					TR	69(74)	59/9	57.5±10.0 (19-75)	≤3/3.1-5 (41/28)	NA	0.39	0.46	1 liver failure, 1 ascites, 27 fever, 50 pain, 42 vomiting
Signoriello 2012 [60]	Retrospective cohort	Italy	HCC	0.1-9	RES	34(44)	30/4	62±7	≤3/3.1-5/>5.1 (13/9/4)	NA	NA	0.29	NA
					RFA	50(74)	40/10	68±7	≤3/3.1-5/>5.1 (24/11/7)	NA	NA	0.15	NA
					PEI	256(349)	188/68	67±8	≤3/3.1-5/>5.1 (143/43/12)	NA	NA	0.20	NA
a. Wang 2012 [61]	Retrospective cohort	China	Early HCC	2.5	RES	52	38/14	≤60 (35)	NA	NA	NA	0.92	NA
					RFA	91	60/31	≤60 (40)		NA	NA	0.73	NA
b. Wang 2012 [62]	Retrospective cohort	China	Early HCC	2.5	RES	208	168/40	≤60 (113)	≤2/2.1-5 (6/202)	NA	NA	0.77	NA
					RFA	254	161/93	≤60 (85)	≤2/2.1-5 (60/194)	NA	NA	0.57	NA
Desiderio 2013 [62]	Retrospective cohort	Italy	HCC	4.3(2.3-5)	RES	52(94)	37/15	65.6±4.8	≤3	0.46	NA	0.46	2 hepatic failure, 1 biliary fistula, 2 hemoperitoneum, 9 ascites
					RFA	44(81)	35/9	64.4±6.5		0.36	NA	0.36	6 pain, 7 fever

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Ding 2013 [63]	Retrospective cohort	China	HCC	2.3±1.3	RFA	85(98)	68/17	58.64±8.52 (40-77)	2.38±0.81 (1.0-4.8)	0.82(3y)	NA	0.82(3y)	1 frequent premature ventricular contractions, 1 liver decompensation
					MWA	113(131)	85/28	59.06±11.68 (30-86)	2.55±0.89 (0.8-5.0)	0.78(3y)	NA	0.78(3y)	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Guo 2013 [64]	Retrospective cohort	China	HCC	2.7	RES	102(129)	94/8	51.5(18-75)	≤3/3.1-5 (75/27)	NA	NA	0.63	5 postoperative hemorrhage, 3 bile leak, 4 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	94(125)	78/16	56(19-75)	≤3/3.1-5 (62/32)	NA	NA	0.50	1 postoperative hemorrhage, 2 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Hasegawa 2013 [65]	Retrospective cohort	Japan	HCC	2.2	RES	5361(6461)	3967/1394	66 (48-77)	2.3 (1.2-3)	0.71	NA	0.71	NA
					RFA	5548(7412)	3569/1979	69 (52-80)	2 (1-3)	0.61	NA	0.61	NA
					PEI	2059(2836)	1303/756	69 (52-80)	1.7 (1-3)	0.56	NA	0.56	NA
Iida 2013 [66]	Retrospective cohort	Japan	HCC	0.1-7.5	Laparoscopic RFA	18(27)	NA	73.5±4.0	2.1±0.5	0.78	NA	0.78	1 abscess

Study Year	Design style	Countr y	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					Laparoscopic MWA	40(56)		70.1±6.6	2.0±0.9	0.78	NA	0.78	1 abscess
Imai 2013 [67]	Retrospective cohort	Japan	HCC	4.1	RES	101	75/26	63.3±9.7	2.14±0.55	0.87	NA	0.87	NA
					RFA	82	46/36	67.6±8.5	1.87±0.50	0.60	NA	0.60	NA
Kim 2013 [68]	Retrospective cohort	Korea	Early HCC	0.1-4.2	RES	47	36/11	58.8±10.7	3.66±0.76	NA	0.85(3y)	0.85(3y)	2 pleural effusion, 2 pneumonia, 1 hepatic failure, 1 hepatic abscess, 1 mechanical ileus
					TR	37	31/6	61.7±11.1	3.46±0.75	NA	0.78(3y)	0.78(3y)	1 bile duct dilatation
Lai 2013 [69]	Retrospective cohort	China	HCC	2.9±1.5	RES	80	55/25	60.8±9.9	2.9±1.1	0.71	NA	0.71	NA
					RFA	31	19/12	63.1±12.8	1.8±0.6	0.84	NA	0.84	NA
Lin 2013 [70]	Retrospective cohort	China	Early HCC	3.4	RFA	658	393/265	64.7±10.5	2.4±1.1 (0.8-9.5)	0.60	0.50	0.55	NA
					PEI	378	243/135	63.5±12.1	2.0±0.9 (0.4-7.0)	0.50	0.28	0.40	NA
Peng 2013 [71]	RCT	China	HCC	0.6-5.2	RFA	95(133)	71/24	55.3±13.3	3.39±1.35	NA	0.59(3y)	0.59(3y)	51 pain, 26 fever, 29 vomiting, 4 ascites, 2 pleural effusion, 1 skin burn, 1 abdominal infection, 1 small intestinal obstruction
					TR	94(137)	75/19	53.3±11	3.47±1.44	NA	0.67(3y)	0.67(3y)	57 pain, 33 fever, 40 vomiting, 5 ascites, 3 pleural effusion, 1 skin burn, 1 bile duct stenosis, 1 gastric hemorrhage

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Tohme 2013 [72]	Retrospective cohort	America	Early HCC	2.4	RES	50(62)	31/19	66.3±1	3.07±1.17	0.48	NA	0.48	3 pleural effusion, 1 pneumonia, 1 myocardial infarction, 2 biloma, 2 ileus, 1 ascites, 1 hyperbilirubinaemia >6, 1 renal insufficiency, 2 encephalopathy
					RFA	60(75)	38/22	65.6±12	2.36±0.94	0.35	NA	0.35	1 oesophagitis, 3 encephalopathy, 1 cholangitis, 2 ascites, 1 renal insufficiency, 1 pneumonia
Wong 2013 [73]	Retrospective cohort	China	Early HCC	0.1-5	RES	46	30/16	55.1±12	2.1±0.6	0.85	NA	0.85	2 fever, 1 increased serum alanine aminotransferase level, 2 atelectasis, 2 biloma
					RFA	36	18/18	63.5±13	1.9±0.6	0.72	NA	0.72	None
Zhang 2013 [74]	Retrospective cohort	China	HCC	2.2±1	RFA	78(97)	64/14	54±10.5 (30-80)	≤3/3.1-5 (47/31)	0.43	0.39	0.41	1 persistent jaundice, 1 biliary fistula
					MWA	77(105)	67/10	54±9.5 (26-76)	≤3/3.1-5 (36/41)	0.58	0.29	0.39	1 hemothorax and intrahepatic hematoma, 1 peritoneal hemorrhage
Abdelaziz 2014 [75]	RCT	Egypt	Early HCC	2.3	RFA	45(52)	31/14	56.8±7.3	2.95±1.03	0.68(1y)	NA	0.68(1y)	2 subcapsular hematoma, 1 thigh burn, 2 pleural effusion
					MWA	66(76)	48/18	53.6±5	2.9±0.97	0.96(1y)	NA	0.96(1y)	1 subcapsular hematoma, 1 abdominal wall skin burn
Shi 2014 [76]	Retrospective cohort	China	HCC	3.8	RES	107(126)	87/20	54.5±9.9	≤3/3.1-5 (37/54)	0.73	0.57	0.60	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					MWA	117(143)	93/24	56.6±9.2	≤3/3.1-5 (40/56)	0.65	0.52	0.52	NA
Yang 2014 [77]	Retrospective cohort	Korea	HCC	0.1-7	RES	52	38/14	55.7±10.6	≤2/2.1-5 (21/31)	0.94	NA	0.94	2 pneumonia, 1 wound infection, 1 biliary anastomotic leak, 1 portal vein thrombosis, 1 nausea, 1 delirium, 4 ascites
					RFA	79	59/20	57.2±9.2	≤2/2.1-5 (36/43)	0.86	NA	0.86	1 vomiting, 1 ascites, 6 abdominal pain, 2 nausea, 1 sinus bradycardia
Zhang 2014 [78]	Retrospective cohort	China	Recurrent HCC	2.7	RES	27(29)	25/2	47±13	3.2±1.0	NA	NA	0.63	NA
					MWA	39(46)	37/2	52±13	2.7±1.1	NA	NA	0.62	NA
Pompili 2015 [79]	Retrospective cohort	Italy	Early HCC	2.8	RFA	136	75/61	68 (41-85)	1.8 (1-2)	0.63	NA	0.63	2 ascites, 1 pleural effusion, 1 hemobilia
					PEI	108	90/18	68.5 (34-86)	1.95 (0.8-2)	0.65	NA	0.65	1 hemobilia, 1 portal vein thrombosis
Xu 2015 [80]	RCT	China	HCC	0.1-3	Laparoscopic RES	45	34/11	58.3±3.1 (26-78)	3.6±0.7 (1-5)	NA	0.38(3y)	0.38(3y)	3 bile leakage, 3 pleural effusion, 2 postoperative hemorrhage
					MWA	45	32/13	57.9±3.4 (27-76)	3.8±0.9 (2-5)	NA	0.33(3y)	0.33(3y)	1 bile leakage, 1 pleural effusion, 1 postoperative hemorrhage

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Agcaoglu O 2013 [92]	Prospective cohort	America	HCC	1.7	RES	94	50/44	61.7 ±1.2	3.7 ±0.2	NA	0.53	0.53	2 pulmonary,2 biliary,2 wound-related,1 intestinal,1 hemorrhagic,2 cardiac , and 1 renal
					RFA	295	196/99	63.4 ±0.7	3.4 ±0.1	NA	0.2	0.2	3 bleeding,2 liver abscess,5 pulmonary,3 renal
Zhou Z 2014 [89]	Retrospective cohort	China	HCC	5	RES	21	15/6	42.2 ±7.6	1.7 ±0.3	0.81	NA	0.81	1 intraperitoneal hemorrhage
					RFA	31	20/11	46.7 ±9.8	1.7 ±0.4	0.81	NA	0.81	2 pleural effusion;2 fever;1 pneumonia;1 biloma
Kim JM 2014 [91]	Retrospective cohort	Korea	HCC	2.8	RES	66	48/18	58.	2.1(0.8-3.0)	0.89	NA	0.89	NA
					RFA	67	52/15	59	1.8 (1.0-2.9)	0.49	NA	0.49	NA
Ko S 2014 [90]	Retrospective cohort	China	HCC	5	RES	12	9/3	71.6 ±4.3	2.9 ±1.4	NA	NA	0.67	NA
					RFA	17	9/8	57.3 ±3.6	2.3 ±1.1	NA	NA	0.35	NA
Kang TW 2015 [88]	Retrospective cohort	Korea	HCC	5	RES	142	107/35	53(28-74)	2(1.1–3.0)	0.90	NA	0.90	1 intra-abdominal abscess,3 wound problem,1 abdominal bleeding,1 intestinal obstruction

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	438	337/101	58(30-80)	1.9(1.1–3.0)	0.85	NA	0.85	3 tumor seeding,2 biloma,2 hepatic abscess,1 bile duct stricture,1 hepatic infarction
Lee YH 2015 [87]	Retrospective cohort	China	HCC	3.63	RES	330	261/69	61 ±12	<5	NA	NA	0.76	NA
					RFA	369	244/125	66 ± 11	<5	NA	NA	0.66	NA
Liu PH 2016 [83]	Prospective cohort	China	HCC	3.7	RES	109	78/31	60 ±13	<2	NA	0.81	0.81	NA
					RFA	128	84/44	64 ±12	<2	NA	0.76	0.76	NA
Hof J 2016 [85]	Retrospective cohort	Netherlands	HCC	3.2	RES	261	151/110	63.4	<5	0.69	NA	0.69	NA
					RFA	75	55/20	65.7	<5	NA	0.33(3y)	0.33(3y)	NA
Lee HW 2018 [81]	RCT	Korea	HCC	5	RES	29	23/6	55.6 ±7.9	<5	NA	0.97(3y)	0.97(3y)	7 pleural effusion
					RFA	34	24/10	56.1 ±7.4	<5	NA	0.97(3y)	0.97(3y)	3 pain

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Li W 2017 [82]	Retrospective cohort	China	HCC	5	RES	220(239)	37/183	61.8 (40-73)	2.1 ±0.5	0.75	NA	0.75	64 complications
					MWA	60(61)	14/46	65(45-71)	2.0 ±0.5	0.67	NA	0.67	13 complications
Vogl TJ 2015 [86]	Retrospective cohort	Germany	HCC	5	RFA	25(32)	19/6	57 ±3.5	3.2(0.8-4.5)	0.72(3y)	NA	0.72(3y)	NA
					MWA	28(36)	23/5	60 ±4.2	3.6(0.9-5)	0.79	NA	0.79(3y)	NA
Liu H 2016 [86]	RCT	China	HCC	4.7	TR	100(114)	86/14	52(31-80)	2.8(0.6-5)	0.67	NA	0.67	8 pleural effusion,5 biliary fstula,4 abdominal ascites,2 liver dysfunction,2 pneumonia,1 wound infection,1 abdominal infection
					RES	100(109)	94/6	49(30-76)	3(0.6-5)	0.84	NA	0.84	4 pleural effusion,3 liver dysfunction,3 abdominal ascites,1 abdominal bleeding

HCC: hepatocellular carcinoma;
BCLC: Barcelona Clinic Liver Cancer;
RES: resection;
RFA: radiofrequency ablation;
MWA: microwave ablation;
TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

RCT: randomized controlled trial;

NA: not available.

Table S2.
Quality assessment of included studies using GRADE framework.

Intervention/Comparator	Illustrative comparative risks* (per 1000, 95% CI)		Relative effect of survival time (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Comparator Assumed survival risk	Corresponding survival risk with intervention			
1-year OS rate					
RES/MWA	923	984 (932 to 997)	**OR 5.25 (1.15 to 23.97)**	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	947	944 (902 to 968)	OR 0.94 (0.52 to 1.71)	990 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	835	802 (674 to 889)	OR 0.80 (0.41 to 1.58)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	944	963 (906 to 1000)	OR 1.02 (0.96 to 1.09)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	932	945 (931 to 956)	OR 1.25 (0.99 to 1.60)	5006 (30 studies)	⊕⊕⊕⊕ high
RES/TR	939	904 (765 to 965)	OR 0.61 (0.21 to 1.79)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	938	802 (310 to 978)	OR 0.27 (0.03 to 2.90)	31 (1 study)	⊕⊕⊖⊖ low
3-year OS rate					

RES/MWA	712	734 (623 to 822)	OR 1.12 (0.67 to 1.87)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	736	779 (717 to 828)	OR 1.26 (0.91 to 1.73)	987 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	499	536 (421 to 645)	OR 1.16 (0.73 to 1.83)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	729	748 (657 to 822)	OR 1.10 (0.71 to 1.71)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	785	851 (823 to 875)	**OR 1.57 (1.28 to 1.93)**	15906 (30 studies)	⊕⊕⊕⊖ moderate
RES/TR	798	760 (618 to 860)	OR 0.80 (0.41 to 1.55)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	737	611 (516 to 704)	OR 0.56 (0.38 to 0.85)	454 (4 studies)	⊕⊕⊕⊖ moderate
5-year OS rate					
RES/MWA	545	607 (492 to 712)	OR 1.29 (0.81 to 2.07)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	545	609 (442 to 756)	OR 1.30 (0.66 to 2.58)	687 (4 studies)	⊕⊕⊖⊖ low
RES/PEI	293	436 (334 to 545)	**OR 1.87 (1.21 to 2.90)**	519 (3 studies)	⊕⊕⊕⊖ moderate
RFA/PEI	533	496 (368 to 624)	OR 0.86 (0.51 to 1.45)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	601	744 (705 to 779)	**OR 1.93 (1.59 to 2.34)**	15154 (25 studies)	⊕⊕⊕⊖ moderate

RES/TR	290	419 (251 to 607)	OR 1.76 (0.82 to 3.78)	117 (1 study)	⊕⊕⊖⊖ low
RFA/TR	464	356 (222 to 523)	OR 0.64 (0.33 to 1.27)	139 (1 study)	⊕⊕⊕⊖ moderate

The absolute and relative risk of survival with treatments*. GRADE: Grading of Recommendations, Assessment, Development and Evaluation. *The results presented in the Table S1 were built around the assumption of a consistent relative effect. The implications of this effect for populations were considered at different baseline risks. Based on the assumed risks, corresponding risks after an intervention were calculated using the meta-analytic risk ratio.

Table S3.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in RCT.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	13			11			5		
RES		2	2.86		1	1.52		1	1.42
RFA		3	3.13		3	2.58		2	2.46
MWA		1	1.04		NA	NA		NA	NA
TR		4	3.59		2	2.35		3	2.89
PEI		5	4.43		4	3.55		4	3.23
3-5cm	4			4			2		
RES		1	1.17		1	1.19		1	1.69
RFA		3	2.88		3	2.91		3	2.60
MWA		NA	NA		NA	NA		NA	NA
TR		2	1.94		2	1.90		2	1.71
PEI		NA	NA		NA	NA		NA	NA
All tumours (⩽	20			16			7		

5cm)						
RES	3	2.53	1	1.85	1	1.62
RFA	4	3.94	4	3.62	3	2.87
MWA	1	1.67	3	2.88	NA	NA
TR	2	1.93	2	2.38	2	1.78
PEI	5	4.92	5	4.27	4	3.73

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S4.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in all studies.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	50			48			37		
RES		3	1.18		1	1.71		1	1.16
RFA		4	3.17		3	3.38		2	3.02
MWA		1	1.91		4	3.42		3	3.11
TR		2	2.63		2	2.73		4	3.61
PEI		5	4.62		5	3.76		5	4.11
3-5cm	19			18			12		
RES		1	1.12		1	1.04		1	1.93
RFA		4	3.54		4	3.58		3	3.18
MWA		3	3.45		3	3.50		4	3.43
TR		2	2.05		2	2.14		2	1.94
PEI		5	4.84		5	4.74		5	4.53

All tumours (≤ 5cm)	72		68		50	
RES	2	2.07	1	1.50	1	1.11
RFA	3	3.48	3	3.68	4	3.34
MWA	4	3.57	4	3.84	3	3.23
TR	1	1.19	2	1.82	2	3.05
PEI	5	4.70	5	4.16	5	4.28

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S5.

Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.97 (0.42-1.98)	0.98 (0.77-1.26)
MWA vs RES	**152 (1.44-505.80)**	NA
TR vs RES	1.08 (0.15-3.78)	0.99(0.67-1.47)
PEI vs RES	0.64 (0.18-1.61)	1.03 (0.54-1.94)
MWA vs RFA	**173.30 (1.90-537.40)**	1.42 (0.63-3.19)
TR vs RFA	1.25 (0.16-4.64)	1.00 (0.56-1.80)
PEI vs RFA	0.67 (0.28-1.35)	0.97 (0.78-1.19)
TR vs MWA	**0.15 (0-0.80)**	NA
PEI vs MWA	**0.08 (0-0.38)**	NA
PEI vs TR	1.17 (0.11-4.66)	NA
3-year OS rate for treatment vs reference		

RFA vs RES	0.75 (0.41-1.31)	0.92 (0.71-1.19)
MWA vs RES	NA	NA
TR vs RES	1.17 (0.16-4.17)	0.80(0.52-1.22)
PEI vs RES	0.58 (0.29-1.16)	1.21 (0.59-2.15)
MWA vs RFA	NA	NA
TR vs RFA	1.54 (0.25-13.43)	1.01 (0.55-1.87)
PEI vs RFA	0.79 (0.45-1.39)	0.91 (0.71-1.17)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.02 (0.14-3.56)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.10-2.47)	0.93 (0.62-1.37)
MWA vs RES	NA	NA
TR vs RES	0.84 (0.03-4.18)	0.88(0.69-1.12)
PEI vs RES	0.50 (0.04-2.04)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	2.87 (0.04-13.43)	NA
PEI vs RFA	0.94 (0.08-3.97)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	3.93 (0.03-19.61)	NA

Table S6.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.25 (0-1.47)	0.89 (0.45-1.77)
MWA vs RES	NA	NA

TR vs RES	1.00 (0-5.0)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.40 (0.64-11.93)	1.10 (0.78-1.55)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.24 (0-1.25)	0.70 (0.34-1.45)
MWA vs RES	NA	NA
TR vs RES	1.14 (0-6.20)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.98 (0.71-15.22)	1.29 (0.87-1.89)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
5-year OS rate for treatment vs reference		
RFA vs RES	1.05 (0.03-5.33)	0.71 (0.32-1.57)
MWA vs RES	NA	NA
TR vs RES	12.87 (0.02-44.43)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	7.64 (0.14-42.49)	1.93 (0.53-7.06)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S7.

Survival rates (1-year, 3-year and 5-year) for lesion (≤5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.57 (0.27-1.08)	0.96 (0.78-1.19)
MWA vs RES	2.01 (0.47-5.70)	0.98 (0.54-1.78)
TR vs RES	1.50 (0.48-3.67)	0.99 (0.67-1.47)
PEI vs RES	**0.37 (0.13-0.82)**	1.03 (0.54-1.94)
MWA vs RFA	3.84 (0.81-11.60)	1.42 (0.63-3.19)
TR vs RFA	**2.69 (1.02-6.04)**	1.09 (0.84-1.43)
PEI vs RFA	0.65 (0.33-1.13)	0.95 (0.80-1.14)
TR vs MWA	1.09 (0.16-3.50)	NA
PEI vs MWA	**0.27 (0.05-0.84)**	NA
PEI vs TR	**0.29 (0.09-0.73)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.65 (0.31-1.29)	0.88 (0.71-1.10)
MWA vs RES	1.00 (0.16-3.30)	0.88 (0.39-1.98)
TR vs RES	0.98 (0.35-2.41)	0.80 (0.51-1.22)
PEI vs RES	0.55 (0.19-1.44)	1.12 (0.59-2.15)
MWA vs RFA	1.77 (0.22-6.24)	NA
TR vs RFA	1.56 (0.66-3.25)	1.20 (0.90-1.60)
PEI vs RFA	0.86 (0.39-1.79)	0.84 (0.66-1.07)
TR vs MWA	1.86 (0.21-7.59)	NA
PEI vs MWA	1.05 (0.12-4.56)	NA
PEI vs TR	0.64 (0.19-1.67)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.66 (0.20-1.62)	0.88 (0.65-1.18)
MWA vs RES	NA	NA

TR vs RES	1.35 (0.23-4.69)	0.80 (0.52-1.22)
PEI vs RES	0.41 (0.11-1.02)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	2.29 (0.41-7.61)	1.30 (0.70-2.41)
PEI vs RFA	0.74 (0.16-2.00)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	0.53 (0.06-1.90)	NA

OR: odds ratio;
RES: resection;
RFA: radiofrequency ablation;
MWA: microwave ablation;
TR: transcatheter arterial chemoembolization and radiofrequency ablation;
PEI: percutaneous ethanol injection;
NA: not available.

Table S8.
Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.94 (0.39-1.91)	1.00(0.95-1.04)
MWA vs RES	1.49 (0.44-3.85)	1.02(0.72-1.43)
TR vs RES	1.30 (0.28-3.88)	1.01(0.74-1.39)
PEI vs RES	0.63 (0.22-1.44)	1.00 (0.93-1.07)
MWA vs RFA	1.59 (0.69-3.17)	1.02 (0.85-1.23)
TR vs RFA	1.48 (0.34-4.23)	1.00(0.56-1.80)
PEI vs RFA	0.68 (0.38-1.09)	0.99 (0.93-1.06)

TR vs MWA	1.08 (0.21-7.87)	NA
PEI vs MWA	0.49 (0.18-1.10)	NA
PEI vs TR	0.69 (0.14-2.13)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.37-1.30)	**0.94 (0.90-0.99)**
MWA vs RES	0.73 (0.30-1.55)	0.95 (0.78-1.18)
TR vs RES	0.90 (0.31-2.10)	1.08 (0.64-1.33)
PEI vs RES	0.68 (0.30-1.39)	1.00 (0.71-1.40)
MWA vs RFA	1.02 (0.57-1.70)	1.00 (0.82-1.22)
TR vs RFA	1.31 (0.47-2.92)	1.01 (0.55-1.87)
PEI vs RFA	0.96 (0.59-1.50)	0.97 (0.90-1.03)
TR vs MWA	1.38 (0.42-3.40)	NA
PEI vs MWA	1.01 (0.47-1.95)	NA
PEI vs TR	0.90 (0.29-2.17)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.54 (0.24-1.05)	**0.85 (0.81-0.90)**
MWA vs RES	0.55 (0.19-1.25)	0.88 (0.61-1.30)
TR vs RES	**0.49 (0.16-0.18)**	0.77 (0.53-1.11)
PEI vs RES	**0.43 (0.17-0.89)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.04 (0.50-1.77)	1.02 (0.78-1.33)
TR vs RFA	0.99 (0.32-2.39)	NA
PEI vs RFA	0.82 (0.48-1.29)	**0.92 (0.85-0.99)**
TR vs MWA	1.03 (0.28-2.73)	NA
PEI vs MWA	0.86 (0.39-1.65)	NA
PEI vs TR	1.07 (0.31-2.72)	NA

Table S9.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)

	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	**0.12 (0-0.63)**	0.96 (0.81-1.14)
MWA vs RES	0.15 (0-1.00)	NA
TR vs RES	0.36 (0.01-2.08)	1.02 (0.55-1.88)
PEI vs RES	**0.06 (0-0.31)**	NA
MWA vs RFA	1.29 (0.32-3.60)	0.99 (0.60-1.64)
TR vs RFA	**2.99 (1.14-6.58)**	1.11 (0.80-1.54)
PEI vs RFA	0.49 (0.18-1.12)	0.89 (0.66-1.20)
TR vs MWA	3.39 (0.58-10.44)	NA
PEI vs MWA	0.55 (0.09-1.76)	NA
PEI vs TR	**0.20 (0.05-0.54)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	**0.11 (0.01-0.40)**	**0.72 (0.60-0.88)**
MWA vs RES	**0.12 (0.01-0.53)**	1.02 (0.57-1.81)
TR vs RES	0.26 (0.01-1.10)	0.92 (0.48-1.75)
PEI vs RES	**0.06 (0-0.28)**	NA
MWA vs RFA	1.15 (0.39-2.65)	0.81 (0.45-1.43)
TR vs RFA	2.38 (0.93-5.38)	1.29 (0.87-1.89)
PEI vs RFA	0.55 (0.12-1.69)	0.71 (0.50-1.00)
TR vs MWA	2.62 (0.61-7.90)	NA
PEI vs MWA	0.61 (0.08-2.26)	NA
PEI vs TR	0.28 (0.04-0.96)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.69 (0.04-3.16)	**0.53 (0.40-0.68)**
MWA vs RES	1.24 (0.02-4.46)	0.90 (0.48-1.69)
TR vs RES	14.31 (0.04-21.06)	NA
PEI vs RES	3.02 (0.01-2.40)	NA
MWA vs RFA	1.26 (0.19-4.04)	0.57 (0.21-1.51)
TR vs RFA	6.16 (0.27-25.58)	2.36 (0.66-8.37)
PEI vs RFA	0.86 (0.06-2.68)	**0.56 (0.37-0.84)**

TR vs MWA	11.97 (0.19-46.76)	NA
PEI vs MWA	4.15 (0.04-5.18)	NA
PEI vs TR	5.77 (0.01-2.84)	NA

Table S10.

Survival rates (1-year, 3-year and 5-year) for lesion (≤ 5cm) treatment comparisons estimated by direct, indirect and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.68 (0.35-1.17)	0.99 (0.95-1.04)
MWA vs RES	0.70 (0.29-1.39)	0.97 (0.77-1.23)
TR vs RES	1.72 (0.66-3.70)	1.01 (0.76-1.33)
PEI vs RES	**0.52 (0.24-0.96)**	1.01 (0.74-1.39)
MWA vs RFA	1.04 (0.55-1.76)	1.01 (0.85-1.20)
TR vs RFA	**2.55 (1.20-4.85)**	1.10 (0.85-1.43)
PEI vs RFA	0.77 (0.51-1.10)	0.98 (0.93-1.05)
TR vs MWA	**2.69 (0.99-6.00)**	0.91 (0.70-1.18)
PEI vs MWA	0.81 (0.38-1.51)	NA
PEI vs TR	**0.34 (0.11-0.63)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.63 (0.37-1.01)	**0.96 (0.94-0.98)**
MWA vs RES	0.62 (0.32-1.09)	0.94 (0.72-1.22)
TR vs RES	0.97 (0.48-1.79)	0.92(0.68-1.24)
PEI vs RES	0.59 (0.30-1.04)	**0.93 (0.86-1.00)**
MWA vs RFA	0.99 (0.64-1.47)	1.05 (0.86-1.26)
TR vs RFA	1.57 (0.89-2.57)	1.20 (0.90-1.60)
PEI vs RFA	0.94 (0.64-1.34)	0.95 (0.89-1.01)
TR vs MWA	1.65 (0.80-3.03)	NA
PEI vs MWA	0.98 (0.55-1.65)	NA

PEI vs TR	0.64 (0.32-1.16)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	**0.52 (0.29-0.88)**	**0.84 (0.80-0.88)**
MWA vs RES	0.55 (0.25-1.05)	0.93(0.78-1.12)
TR vs RES	0.59 (0.25-1.20)	0.69 (0.34-1.42)
PEI vs RES	**0.45 (0.23-0.82)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.06 (0.64-1.61)	0.97 (0.75-1.25)
TR vs RFA	1.16 (0.54-2.21)	1.30 (0.70-2.41)
PEI vs RFA	0.87 (0.57-1.26)	**0.91 (0.84-0.98)**
TR vs MWA	1.16(0.46-2.46)	NA
PEI vs MWA	0.87 (0.46-1.51)	NA
PEI vs TR	0.84 (0.35-1.74)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S11.

Posterior summaries from random effects consistency and inconsistency models for small lesion (<3cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.55	0.21	(0.15-1.00)	0.38	0.23	(0.02-0.88)
τ	12.40	65.04	(1.10-45.68)	109.40	620.40	(1.30-940.00)
resdev	90.04	13.04	(66.16-117.10)	94.65	12.94	(70.06-120.70)

pD	66.48			57.5		
DIC	453.18			404.59		
3-year OS rate for treatment vs reference						
σ	0.59	0.14	(0.34-0.88)	0.6	0.14	(0.36-0.91)
τ	3.26	1.62	(1.34-7.33)	3.28	1.90	(1.19-8.10)
resdev	92.02	14.19	(66.64-122.10)	90.7	13.92	(65.64-120.00)
pD	80.45			71.83		
DIC	589.01			517.44		
5-year OS rate for treatment vs reference						
σ	0.53	0.12	(0.32-0.80)	0.55	0.13	(0.34-0.84)
τ	4.06	2.02	(1.66-8.76)	3.80	2.05	(1.40-8.77)
resdev	63.99	11.47	(43.52-88.24)	63.55	11.37	(43.39-87.90)
pD	64.22			55.07		
DIC	488.23			412.10		

Table S12.
Posterior summaries from random effects consistency and inconsistency models for lesion (3-5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.28	0.25	(0.01-0.92)	0.38	0.34	(0.02-1.28)
τ	3108.00	68630.00	(1.44-4879.00)	19500.00	720600.00	(0.62-4178.00)
resdev	28.90	6.96	(17.25-44.41)	484.70	5117	(0.63-2616)
pD	24.70			24.62		
DIC	166.90			157.30		
3-year OS rate for treatment vs reference						
σ	0.62	0.27	(0.17-1.24)	0.67	0.31	(0.14-1.40)
τ	5.34	12.61	(0.83-21.20)	41.87	585.80	(0.52-77.13)
resdev	32.36	8.17	(18.39-50.07)	32.62	8.22	(18.52-50.51)

pD	30.91			28.63		
DIC	212.30			188.69		
5-year OS rate for treatment vs reference						
σ	0.80	0.46	(0.14-1.94)	0.60	0.42	(0.04-1.64)
τ	337.00	11980	(0.30-20.22)	10100.00	258400.00	(0.37-691.30)
resdev	22.54	6.73	(11.29-37.43)	22.57	6.519	(11.45-36.90)
pD	22.61			19.88		
DIC	146.84			131.53		

Table S13.

Posterior summaries from random effects consistency and inconsistency models for lesion (≤ 5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.49	0.13	(0.26-0.77)	0.29	0.14	(0.05-0.58)
τ	6.00	6.24	(1.92-16.85)	116.80	1122.00	(2.96-419.40)
resdev	129.2	14.99	(101.40-160)	133.1	14.50	(105.70-162.80)
pD	95.71			78.20		
DIC	692.39			604.18		
3-year OS rate for treatment vs reference						
σ	0.50	0.09	(0.33-0.70)	0.47	0.096	(0.29-0.67)
τ	4.20	1.45	(2.15-7.71)	5.31	2.59	(2.24-11.80)
resdev	124	15.64	(95.16-156.40)	124.5	15.89	(95.35-157.50)
pD	111.54			93.41		
DIC	856.01			723.74		
5-year OS rate for treatment vs reference						
σ	0.44	0.10	(0.26-0.65)	0.44	0.1	(0.26-0.67)
τ	5.30	2.27	(2.38-14.90)	6.09	3.95	(2.29-14.87)

resdev	86.73	13.53	(62.35-115.40)	85.74	13.55	(61.39-114.40)
pD	84.53			68.81		
DIC	670.73			544.40		

sd: standard deviation;

CI: Credible Interval

σ: between-trial standard deviation

τ^2: between-trial variance

resdev: residual deviance

pD: effective number of parameters

DIC: deviance information criterion

Figure S1.

Results of the consistency test for closed loop at 1-year, 3-year, and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm.

i Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm ii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm

iii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm

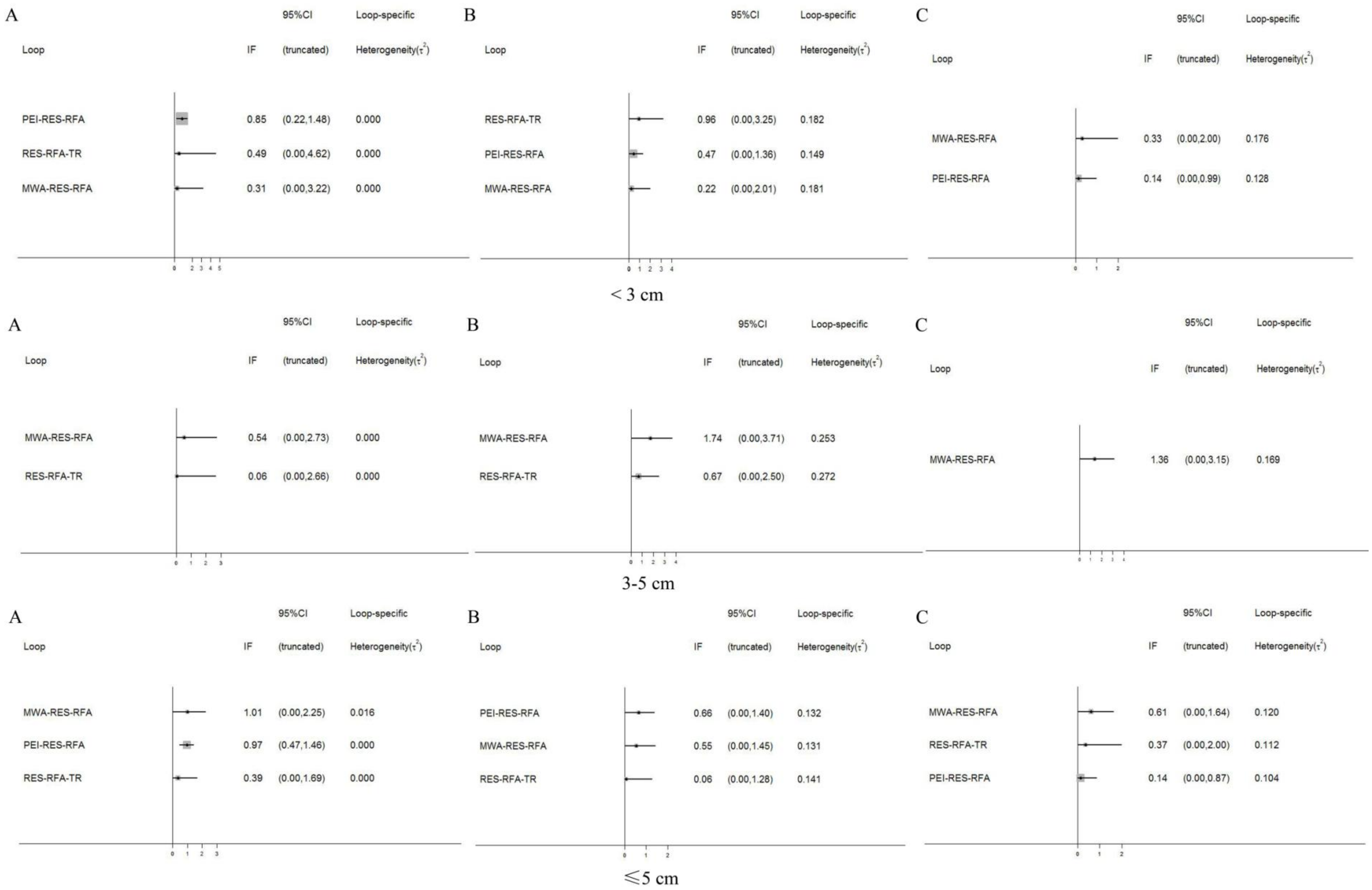

A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.85 (0.22,1.48) 0.000
RES-RFA-TR 0.49 (0.00,4.62) 0.000
MWA-RES-RFA 0.31 (0.00,3.22) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
RES-RFA-TR 0.96 (0.00,3.25) 0.182
PEI-RES-RFA 0.47 (0.00,1.36) 0.149
MWA-RES-RFA 0.22 (0.00,2.01) 0.181
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.33 (0.00,2.00) 0.176
PEI-RES-RFA 0.14 (0.00,0.99) 0.128
< 3 cm
A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.54 (0.00,2.73) 0.000
RES-RFA-TR 0.06 (0.00,2.66) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.74 (0.00,3.71) 0.253
RES-RFA-TR 0.67 (0.00,2.50) 0.272
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.36 (0.00,3.15) 0.169
3-5 cm
A
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.01 (0.00,2.25) 0.016
PEI-RES-RFA 0.97 (0.47,1.46) 0.000
RES-RFA-TR 0.39 (0.00,1.69) 0.000
B
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.66 (0.00,1.40) 0.132
MWA-RES-RFA 0.55 (0.00,1.45) 0.131
RES-RFA-TR 0.06 (0.00,1.28) 0.141
C
Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.61 (0.00,1.64) 0.120
RES-RFA-TR 0.37 (0.00,2.00) 0.112
PEI-RES-RFA 0.14 (0.00,0.87) 0.104
≤5 cm

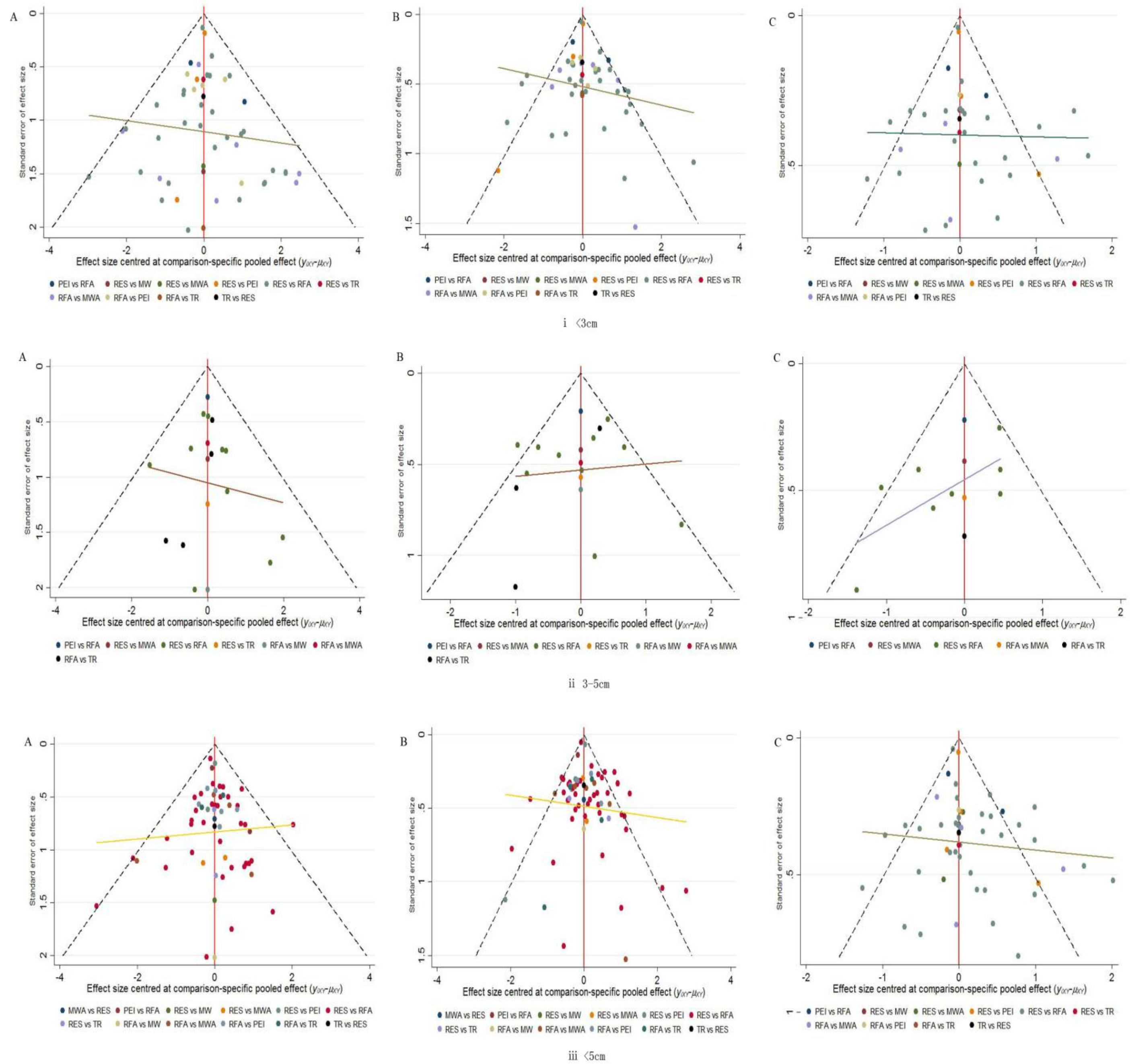
Figure S2.

Assessment of publication bias using funnel plot.

i Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm.

ii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm.

iii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm


A
B
C
Standard error of effect size
Effect size centred at comparison-specific pooled effect ($y_{iXY}-\mu_{XY}$)
PEI vs RFA RES vs MW RES vs MWA RES vs PEI RES vs RFA RES vs TR
RFA vs MWA RFA vs PEI RFA vs TR TR vs RES
i <3cm
PEI vs RFA RES vs MWA RES vs RFA RES vs TR RFA vs MW RFA vs MWA
RFA vs TR
PEI vs RFA RES vs MWA RES vs RFA RFA vs MWA RFA vs TR
ii 3-5cm
MWA vs RES PEI vs RFA RES vs MW RES vs MWA RES vs PEI RES vs RFA
RES vs TR RFA vs MW RFA vs MWA RFA vs PEI RFA vs TR TR vs RES
PEI vs RFA RES vs MW RES vs MWA RES vs PEI RES vs RFA RES vs TR
RFA vs MWA RFA vs PEI RFA vs TR TR vs RES
iii <5cm

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8

METHODS

Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	11,12
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11,12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11,12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Palliative care, Radiology and imaging, Surgery
Keywords:	resection, radiofrequency ablation, microwave ablation, transcatheter arterial chemoembolization, percutaneous ethanol injection, hepatocellular carcinoma

Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis

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[τ]Lanjuan Li, and Hongcui Cao contributed equally to this paper.

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Number of figures and tables: 7 figures and 15 tables

List of abbreviations in order of appearance: HCC: hepatocellular carcinoma; RES: resection; RFA: radiofrequency ablation; MWA: microwave ablation; TACE: transcatheter arterial chemoembolization; PEI: percutaneous ethanol injection; GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TR: TACE plus RFA; OS: overall survival; MCMC: Markov Chain Monte Carlo; CrI: credible interval; SUCRA: surface under the cumulative ranking curve LPS: lipopolysaccharide; TNFα: tumor necrosis factor α; IL: interleukin; TGFβ: transforming growth factor β.

Conflict of interest: The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement: No additional data are available.

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Author Contributions:

1. Conceived and designed the experiments: Hongcui Cao, Tian’an Jiang, Lanjuan Li

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3. Analyzed the data: Guo Tian, Shigui Yang, Jinqiu Yuan, Qiyu Zhao

4. Contributed reagents/materials/analysis tools: Qiyu Zhao, Fen Chen

5. Wrote the manuscript: Guo Tian, Shigui Yang, Tian'an Jiang

6. Critically revised and approved the final version of manuscript: Diane Threapleton, Hongcui Cao, Tian'an Jiang, Lanjuan Li

7. Study supervision: Hongcui Cao, Tian'an Jiang, Lanjuan Li

Abstract

Objective: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide. We conducted network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

Methods and analyses: We pooled the odds ratio (OR) for 1-, 3- and 5-year overall survival, based on lesions of size < 3 cm, 3-5 cm and ≤ 5 cm, using five therapeutic options including resection (RES), radiofrequency ablation (RFA), microwave ablation (MWA), transcatheter arterial chemoembolization (TACE) plus RFA (TR) and percutaneous ethanol injection (PEI).

Results: We identified 74 studies, including 26944 patients. After adjustment for study design, and in the full sample of studies, the treatments were ranked in order of greatest to least benefit as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI. The ranks were similar for 1 and 3-year survival, with RES and TR being the highest ranking treatments. In both smaller (<3cm) and larger tumors (3-5cm), RES and TR were also the two highest ranking treatments. There was little evidence of inconsistency between direct and indirect evidence.

Conclusion: The comparison of different treatment strategies for HCC indicated that RES is associated with longer survival. However, many of the between-treatment comparisons were not statistically significant and, for now, selection of strategies for treatment will depend patient and disease characteristics. Additionally, much of the evidence was provided by non randomised studies and knowledge gaps still exist.

More head-to-head comparisons between both RES and TR, or other approaches, will be necessary to confirm these findings.

Key words: resection; radiofrequency ablation; microwave ablation; transcatheter arterial chemoembolization; percutaneous ethanol injection; hepatocellular carcinoma.

Strengths and limitations of this study:

1. This is a network meta-regression within a bayesian framework to compare and rank different treatment strategies for HCC through direct and indirect evidence from international studies.

2. Strong and reliable methodological and statistical procedures were applied.

3. The individual or tumor characteristics within HCC articles would be a source of heterogeneity..

4. A major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival.

5. Other studies did not report the primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies.

Introduction

Cancer was the second leading cause of death in 2013, behind cardiovascular disease, and in 2013 more than 8 million people died from cancer globally [1-3]. Hepatocellular carcinoma (HCC) was the 6th most common cancer worldwide and the 3rd leading cause of cancer death, with 5-year overall survival rates under 12% [4 5].

Hepatic resection (RES) was the traditional choice for patients with HCC, without cirrhosis and with good remaining liver function [6]. Despite nearly 70% 5-year survival, recurrence rates after surgery were high [7]. Repeated hepatectomies to lengthen survival were not often appropriate owing to multiple-site tumor recurrence or patient background of liver cirrhosis [8 9]. Many locoregional therapies have been developed including ablative treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), or microwave ablation (MWA), and trans-arterial therapies such as transcatheter arterial chemoembolization (TACE) or transarterial chemotherapy infusion (TACI). Locoregional therapies were minimally invasive and therefore are cheaper and faster to recover, as compared to resection. Such approaches may be appropriate for patients with unresectable, small or multiple carcinomas or those with severe cirrhosis. However, there may be a greater risk of recurrence because of incomplete destruction of cancer cells at the treatment margin, as seen with RFA [10].

Selection of treatment strategy was determined by liver function, tumor stage and patient performance status [7], but much uncertainty still remains surrounding the comparative efficacy of different treatment approahces. A recent review of international guidelines for HCC found similarities but also some discrepancy in treatment allocation recommendations because of regional classification differences, secondary to a lack of solid or high-level evidence [11]. A recent review of therapies also revealed that there was no consensus on whether surgery or ablation was better for small tumors [7]. Some discrepancy in prevalence and treatment outcomes may be still in different regions because of local biology, available resources or expertise and access to care [11]. However, if we ever hope to achieve standardized and evidence-based therapy for HCC, the unanswered question surrounding relative treatment efficacy of RES compared to ablative locoregional therapies should be resolved.

Traditional meta-analysis is limited by existing head-to-head treatment comparisons within included studies. It is therefore not possible to gauge the relative benefit of two treatments that have never been directly compared in studies. Real-life treatment decisions are hindered by gaps in existing evidence, but network meta-analysis enables integration of direct and indirect comparisons to provide estimates for relative comparisons across many treatments [12]. Recent published network meta-analysis focused on advanced HCC by TACE alone or combined treatments[13 14], as well as antineoplastic drugs (sorafenib, erlotinib, linifanib, sunitinib and brivanib)[15], and early- or very early-stage HCC via surgery or thermal ablation[16]. However, in this study, we included the latest literature, and focused on the comparison of interventional and surgical treatments, including RES, RFA, MWA, and TACE plus RFA (TR), PEI using subgroup analysis of tumor size (smaller: <3cm;

larger: 3-5cm), and study design (cohort or RCT). In order to investigate comparative effectiveness among RES and common locoregional ablative therapies, we performed a strong and reliable bayesian network meta-analysis.

Search Strategy

We conducted a systematic review and report findings in accordance with PRISMA for Network Meta-Analyses (PRISMA-NMA) [17] (Additional file 1: Text S1). The following databases were searched: PubMed, Embase, Web of science and Scopus, up to May 2018, using these keywords: resection, surgery, hepatectomy, radiofrequency ablation, transarterial chemoembolization, microwave thermal ablation, ethanol injection, liver, cancer, tumor (Additional file 1: Text S2). No language restrictions were used. Bibliographies from other relevant review articles were cross-examined for potential missed studies. Disagreement was resolved by a third reviewer. Citations were downloaded into reference management software and duplicate citations were electronically or manually removed.

We systematically included the studies using the following criteria: 1) original data from prospective or retrospective cohort studies and randomized clinical trials (RCTs) in humans; 2) reporting at least two treatments, including resection or any local ablative therapy (RES, RFA, MWA, PEI, or TACE+RFA (TR)); 3) mean lesion size ≤ 5 cm; 4) evaluating overall survival rate not less than one year after first or recurrent treatments. Conference abstracts and case reports were excluded, as were older publications from studies with multiple publications.

Patients and public involvement

The patients or public were not involved in the study.

Data Extraction and Study Quality

Two investigators independently extracted and cross-checked the data from the eligible studies: author, year, study design, country, disease type, inclusion criteria, treatment style, study size, gender, age, tumor size, follow-up duration, treatment complications and survival outcomes. If in disagreement, a third reviewer adjudicated. The level of evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance [18], which was classified into four levels of high, moderate, low, and very low. The quality score was downgraded according to 5 domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias while scores were upgraded according to large effect, appropriate control for plausible confounding, and dose-response gradient.

Data Analysis

Network meta-analysis was used if a ring or open evidence loop was available to know the number of arms and the sample size of each intervention. When possible, pair-wise direct head-to-head comparisons were conducted to calculate the odds ratio (OR) of 1-, 3- and 5-year survival and their 95% confidence intervals (CI).

Between-study heterogeneity was evaluated using the tau-squared statistic (τ^2) [19]. A node-splitting analysis was applied to check the consistency between direct evidence (existing real reported comparisons) and indirect evidence (estimated treatment comparisons) for their agreement on a specific node [20]. Bayesian network meta-analysis with Markov Chain Monte Carlo (MCMC), through a consistency model, was utilized to estimate the pooled ORs and its 95% credible interval (CrI) for the direct and indirect comparisons [16]. The inconsistency model was used to check for heterogeneity due to chance imbalance in the distribution of effect modifiers. Consistency in every closed loop was checked by the loop-specific approach in order to estimate whether treatment survival effects were disturbed by variance in the distribution of potential confounding factors among the studies. In order to compare and rank survival rates of different treatments, we examined all studies first and then separately assessed smaller (<3cm) and larger (3-5cm) tumors. Random-effect meta-regression models were used, with and without adjustment for study design (cohort or RCT) and subgroup analyses were also conducted for RCTs in order to examine treatment effectiveness. We appraised the ranking probabilities for all therapies for each intervention and the treatment hierarchy was ordered by the surface under the cumulative ranking curve (SUCRA) [21]. Sensitivity analysis was conducted to remove each study, in turn, and estimate the treatment effect in the remaining studies. Funnel plots were utilized to check the possible presence of publication bias or small-study bias [22]. In this study, we used Bayesian MCMC simulations by WinBUGS 1.4 and graphically presented the results using Stata 13.

Results

Study Characteristics

After screening, 74 relevant studies in 73 articles were identified, of which 20 were randomized controlled trials and 54 were cohort studies [23-96]. We excluded 136504 duplicate or non-relevant citations (Figure 1). The summary characteristics of these studies are shown in Additional file 1: Table S1. Overall, 32345 patients of mean age from 46 to 73.5 years, with approximately 29236 tumors, were assigned to receive RES, RFA, MWA, TR and PEI, and the mean follow-up ranged from 1.5 to 5.7 years. In addition, the numbers of connected studies to the lines (black) and sample size of each treatment (red) were shown in Figure 2 and 3, respectively.

Network Meta-Analysis Results

Ten possible treatment comparisons among the five interventions were examined in the included studies. Comparable survival estimates were made for each treatment (per 1000 patients) and the survival OR among each of the treatment comparisons, according to follow-up duration, are presented in Additional file 1: Table S2, along with estimation of the quality of evidence using GRADE criteria.

Across the range of treatment comparisons and follow-up durations, evidence was graded between low and high quality. Evidence was often graded as low quality owing to publication bias and graded as high quality owing to a larger number of participants in direct comparisons.

Survival probabilities (estimated using Meanrank) and ranks for the five treatments in patients with tumors <3cm, 3-5cm or ≤5cm (with and without adjustment for study design) are graphically displayed in Figures 2-5, and numerical details are given in Additional file 1: Table S3-S4. RES was consistently associated with greater survival (rank 1) compared to MWA, RFA, TR and PEI for the 5-year survival estimates. The ranks were similar for 1 and 3-year survival with RES or TR being ranked as 1 or 2 in most analyses. After adjustment for study design, and in the full sample of available studies (n=74), the treatments were ranked as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI (Table S4).

Efficacy comparisons from network meta-regression for all treatments are summarized in Table 1 and 2, according to follow-up duration and initial tumor size. Compared to RES, the 5-year survival in all studies (trials and observational studies) for all tumors ≤5cm, was 0.45 (95%CrI 0.23 to 0.82) for PEI, 0.59 (95%CrI 0.25 to 1.20) for TR, 0.55 (95%CrI 0.25 to 1.05) for MWA and 0.52 (95%CrI 0.29 to 0.88) for RFA (Table 2). When examining the comparisons across all treatments, the only significant difference for tumors <3cm was for 5-year survival, and a significantly worse survival was observed for PEI compared to RES 0.43 (95%CrI 0.17 to 0.89). For tumors between 3 and 5 cm, no significant differences were observed at 5-year survival, but significantly worse 3-year survival was observed with PEI, MWA and RFA compared to RES (Table 2). Despite smaller number of studies in analyses of only RCTs, the pairwise comparisons showed similar results. However, all relative rankings should be interpreted with caution because most network meta-regression comparisons did not suggest a statistically significant difference between treatments. Detailed results of each comparison for survival rates were shown in Additional file 1: Table S5-S10**.**

Loop-specific methods detected no inconsistency between the pairwise and network meta-analysis for most closed loops in the network (Additional file 1: Figure S1). However, inconsistency was observed between direct and indirect comparisons for the following loops: lesions <3cm: RES-RFA-TR, PEI-RES-RFA, MWA-RES-RFA; lesions 3-5cm: MWA-RES-RFA, RES-RFA-TR; and lesions ≤5cm: RES-RFA-TR). In addition, tests for inconsistency were carried out (Additional file 1: Table S11-S13), which indicated a close relationship of between-trial heterogeneity and inconsistency between "direct" and "indirect" evidence.

Sensitivity Analysis and publication bias

No significant change was observed when any one study was deleted. Funnel plots indicated that the included studies in each group were distributed symmetrically around the vertical line (x=0), suggesting that no obvious evidence of publication bias or small-sample effect existed in this network (Additional file 1: Figure S2).

Discussion

There were many techniques for attaining a large ablated zone and complete necrosis of HCC and this comprehensive review addressed two of the more common treatments, namely resection and ablation. In this network meta-analysis, of the five examined therapies, the pooled data showed RES ranked best in full sample analysis with or without adjustment for study design. In both smaller (<3cm) and larger tumors (3-5cm) RES remained the highest ranking treatment. However, most of the individual treatment comparisons were not statistically significant and thus, RES may not be superior to all other therapies. Our evidence indicated locoregional therapies and particularily RES or TR (TACE+RFA) were associated with longer survival.

Our observation of better survival outcomes with TR may be through the advantage of dual mechanisms. With TR, TACE induced hypoxic injury on cancer cells through occlusion of blood vessels and was followed by local ablation. This combination therapy may result in a larger ablated zone [97], reducing the possibility of micrometastasis and recurrence, and thus, resulting in better survival outcomes than RFA alone.

While being more invasive, and despite risk of complications, RES was associated with better survival outcomes after 1 year, 3 years and 5 years. This may be due to removal of larger sections of liver than can be targeted with locoregional therapies, thus removing a larger area of potentially cancerous cells. Additionally, rat models indicated that the liver has the potential to quickly restore its original size after partial hepatectomy. This may be mediated via interactions of lipopolysaccharide (LPS), tumor necrosis factor (TNF)α, interleukin (IL)-6, and transforming growth factor β (TGFβ) [98]. However, evidence from rat models and human studies indicated that resection success was associated with resection size and regeneration was stunted with larger resections [99-101]. The safe limit for remnant liver volume in normal liver was approximately 30% of total liver volume, but this was estimated to rise to

40-50% in those with liver disease [99 102]. Liver resection was recognised as the most efficient treatment for HCC but was only applicable for less than 30% of all patients. However, developments in preoperative imaging tachniques, laproscopic surgery and newly developing combinations with chemotherapy may extend its application to more advanced tumors [102]. Furthermore, the consistent associations observed with all studies and only in RCTs indicated that patient selection bias in the observational studies does not wholly explain the better survival outcomes with RES.

Overall, we found PEI was associated with shorter survival than the other four therapies, a finding which is supported in previous studies [24 33]. One study reported RFA was superior to PEI in achieving short- and long-term survival outcomes, although PEI and RFA showed similar 5-year survival in lesions <3 cm [55]. The possible reason why PEI is less effective than RFA may be because lesions often have a thick capsule and therefore ethanol may not distribute through tissues.

There are several limitations in this study. Firstly, a major limitation is in the inclusion of non-randomised studies, in which selection bias is likely to confound observations. Selection of treatment is likely to be based on individual or tumor characteristics, and thus these factors will bias and confound observations of survival. Secondly, this study included both RCTs and observational studies, in which study designs and type of data collection may not be comparable. However, findings were consistent among both study designs. Thirdly, all included studies did not report our primary outcome of interest (5-year survival) and this was a particular limitation among randomised studies. Fourthly, for many individual comparisons, there were either no direct comparisons or comparisons from only a small number of studies. The lack of evidence may increase the risk of bias, which could enlarge or undervalue effect size, and may explain the small inconsistency seen between direct and estimated comparisons. Thus, we should be cautious in interpreting treatment rankings for the different survival times and for different size lesions. While adverse events from treatments may differ (not evaluated in detail in this review), by examining overall survival outcomes in our review, we have taken account of both long-term potential benefits and harms from treatments. The focus of these findings should therefore be on the overall observation that RES or TR may be superior in terms of survival, rather than focusing on specific OR values for individual treatment comparions.

In conclusion, the findings of the current bayesian network meta-analysis indicate that RES or TR may be among the most effective therapeutic approaches for HCC for 5-year survival in both smaller (< 3cm) and larger (3-5cm) lesions. However, evidence was of variable quality, and the majority of evidence came from non randomised studies, which are prone to selection bias and knowledge gaps still exist. For not, at the individual level, selection of strategies should depend on patient and clinical characteristics. To facilitate generation of evidence-based recommendations for HCC therpy, and to standardize treatment approaches, further head-to-head comparisons, especially of resection and ablative therapies, are required from high-quality RCTs, with long follow-up for survival outcomes.

Conflict of interests

The authors have declared that no competing interests regarding the publication of this paper.

Data sharing statement

No additional data are available.

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File legends:

Figure 1 Flow chart of search.

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according

to lesion size in RCTs

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.

A Lesions < 3 cm

B Lesions 3-5 cm

C Lesions ≤ 5 cm (full sample).

Table 1 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in randomized controlled trials.

〈3cm for 1-year survival

PEI				
1.17 (0.11-4.66)	TR			
0.08 (0-0.38)	**0.15 (0-0.80)**	MWA		
0.67 (0.28-1.35)	1.25 (0.16-4.64)	**173.30 (1.90-537.40)**	RFA	
0.64(0.18-1.61)	1.08 (0.15-3.78)	**152.70 (1.44-505.80)**	0.97 (0.42-1.98)	RES

〈3cm for 3-year survival

PEI				
1.02 (0.14-3.56)	TR			
NA	NA	MWA		
0.79 (0.45-1.39)	1.54 (0.25-13.43)	NA	RFA	
0.58 (0.29-1.16)	1.17 (0.16-4.17)	NA	0.75 (0.41-1.31)	RES

〈3cm for 5-year survival

PEI				
3.93 (0.03-19.61)	TR			
NA	NA	MWA		
0.94 (0.08-3.97)	2.87 (0.04-13.43)	NA	RFA	
0.50 (0.04-2.04)	0.84 (0.03-4.18)	NA	0.72 (0.10-2.47)	RES

3-5cm for 1-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.40 (0.64-11.93)	NA	RFA	
NA	1.00 (0-5.00)	NA	0.25 (0-1.47)	RES

3-5cm for 3-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	3.98 (0.71-15.22)	NA	RFA	
NA	1.14 (0-6.20)	NA	0.24 (0-1.25)	RES

3-5cm for 5-year survival

PEI				
NA	TR			
NA	NA	MWA		
NA	7.64 (0.14-42.49)	NA	RFA	
NA	12.87 (0.02-44.43)	NA	1.05 (0.03-5.33)	RES

≤5cm for 1-year survival

PEI				
0.29 (0.09-0.73)	TR			
0.27 (0.05-0.84)	1.09 (0.16-3.50)	MWA		
0.65 (0.33-1.13)	**2.69 (1.02-6.04)**	3.84 (0.81-11.60)	RFA	
0.37 (0.13-0.82)	1.50 (0.48-3.67)	2.01 (0.47-5.70)	0.57 (0.27-1.08)	RES

≤5cm for 3-year survival

PEI				
0.64 (0.19-1.67)	TR			
1.05 (0.12-4.56)	1.86 (0.21-7.59)	MWA		
0.86 (0.39-1.79)	1.56 (0.66-3.25)	1.77 (0.22-6.24)	RFA	
0.55 (0.19-1.44)	0.98 (0.35-2.41)	1.00 (0.16-3.30)	0.65 (0.31-1.29)	RES

≤5cm for 5-year survival

PEI				
0.53 (0.06-1.90)	TR			
NA	NA	MWA		
0.74 (0.16-2.00)	2.29 (0.41-7.61)	NA	RFA	
0.41 (0.11-1.02)	1.35 (0.23-4.69)	NA	0.66 (0.20-1.62)	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

Table 2 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in all studies

〈3cm for 1-year survival

PEI				
0.69 (0.14-2.13)	TR			
0.49 (0.18-1.10)	1.08 (0.21-7.87)	MWA		
0.68 (0.38-1.09)	1.48 (0.34-4.23)	1.59 (0.69-3.17)	RFA	
0.63 (0.22-1.44)	1.30 (0.28-3.88)	1.49(0.44-3.85)	0.94 (0.39-1.91)	RES

〈3cm for 3-year survival

PEI				
0.90 (0.29-2.17)	TR			
1.01 (0.47-1.95)	1.38 (0.42-3.40)	MWA		
0.96(0.59-1.50)	1.31 (0.47-2.92)	1.02 (0.57-1.70)	RFA	
0.68 (0.30-1.39)	0.90 (0.31-2.10)	0.73 (0.30-1.55)	0.72 (0.37-1.30)	RES

〈3cm for 5-year survival

PEI				
1.07 (0.31-2.72)	TR			
0.86 (0.39-1.65)	1.03 (0.28-2.73)	MWA		
0.82 (0.48-1.29)	0.99 (0.32-2.39)	1.04 (0.50-1.77)	RFA	
0.43 (0.17-0.89)	**0.49 (0.16-0.18)**	0.55 (0.19-1.25)	0.54 (0.24-1.05)	RES

3-5cm for 1-year survival

PEI				
0.20 (0.05-0.54)	TR			
0.55 (0.09-1.76)	3.39 (0.58-10.44)	MWA		
0.49 (0.18-1.12)	**2.99 (1.14-6.58)**	1.29 (0.32-3.60)	RFA	
0.06 (0-0.31)	0.36 (0.01-2.08)	0.15 (0-1.00)	**0.12 (0-0.63)**	RES

3-5cm for 3-year survival

PEI				
0.28 (0.04-0.96)	TR			
0.61 (0.08-2.26)	2.62 (0.61-7.90)	MWA		
0.55 (0.12-1.69)	2.38 (0.93-5.38)	1.15 (0.39-2.65)	RFA	
0.06 (0-0.28)	0.26 (0.01-1.10)	**0.12 (0.01-0.53)**	**0.11 (0.01-0.40)**	RES

3-5cm for 5-year survival

PEI				
5.77 (0.01-2.84)	TR			
4.15 (0.04-5.18)	11.97 (0.19-46.76)	MWA		
0.86 (0.06-2.68)	6.16 (0.27-25.58)	1.26 (0.19-4.04)	RFA	
3.02 (0.01-2.40)	14.31 (0.04-21.06)	1.24 (0.02-4.46)	0.69 (0.04-3.16)	RES

≤5cm for 1-year survival

PEI				
0.34 (0.11-0.63)	TR			
0.81 (0.38-1.51)	2.69 (0.99-6.00)	MWA		
0.77 (0.51-1.10)	**2.55 (1.20-4.85)**	1.04 (0.55-1.76)	RFA	
0.52 (0.24-0.96)	1.72 (0.66-3.70)	0.70 (0.29-1.39)	0.68 (0.35-1.17)	RES

≤5cm for 3-year survival

PEI				
0.64 (0.32-1.16)	TR			
0.98 (0.55-1.65)	1.65 (0.80-3.03)	MWA		
0.94 (0.64-1.34)	1.57 (0.89-2.57)	0.99 (0.64-1.47)	RFA	
0.59 (0.30-1.04)	0.97 (0.48-1.79)	0.62 (0.32-1.09)	0.63 (0.37-1.01)	RES

≤5cm for 5-year survival

PEI				
0.84 (0.35-1.74)	TR			
0.87(0.46-1.51)	1.16 (0.46-2.46)	MWA		
0.87 (0.57-1.26)	1.16 (0.54-2.21)	1.06 (0.64-1.61)	RFA	
0.45 (0.23-0.82)	0.59 (0.25-1.20)	0.55 (0.25-1.05)	**0.52 (0.29-0.88)**	RES

The reference treatment (1.00) for all comparisons is listed to the right hand side

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

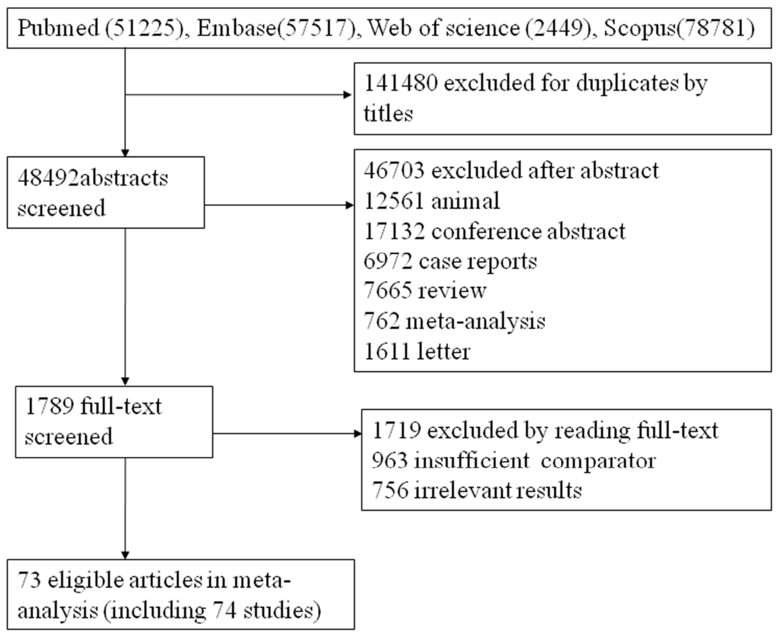

Figure 1 Flow chart of search.

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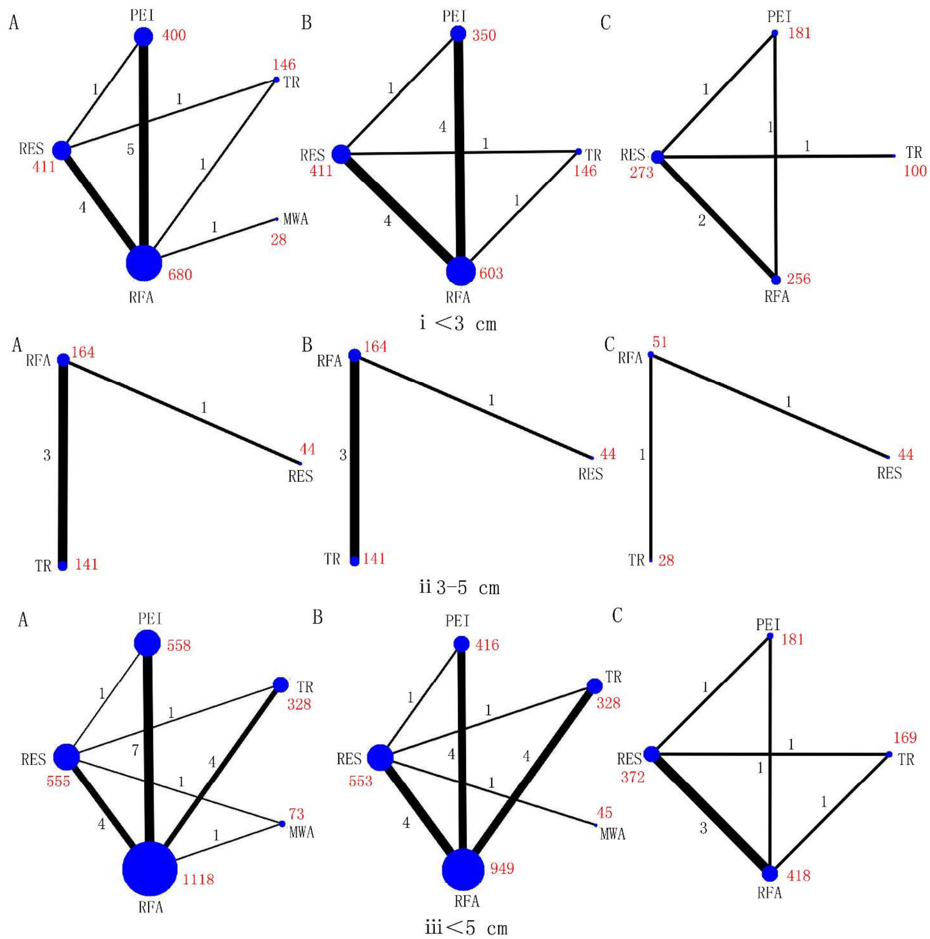

Figure 2 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in RCTs.
Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.
i Lesions < 3 cm.
ii Lesions 3-5 cm.
iii Lesions ≤ 5 cm.

500x500mm (300 x 300 DPI)

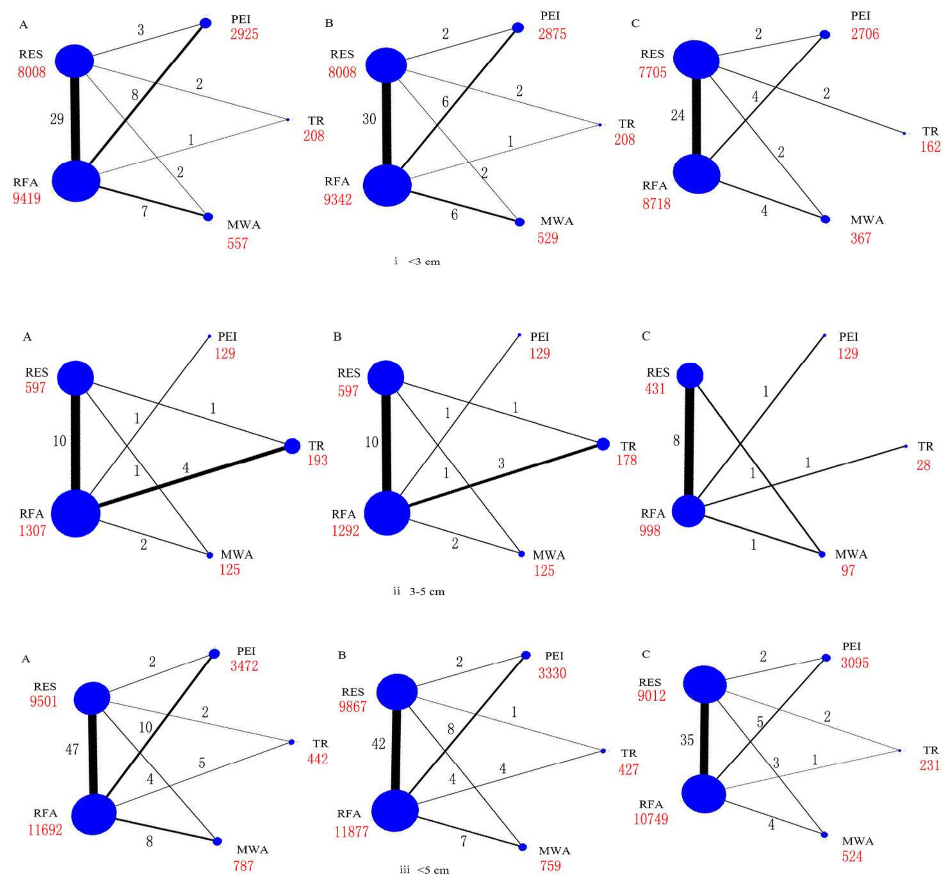

Figure 3 Networks of treatment comparisons for 1-year (A), 3-year (B), and 5-year (C) survival rates in all studies.

Circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. The number in red indicates the sample size and the number in black indicates the number of studies.

i Lesions < 3 cm.

ii Lesions 3-5 cm.

iii Lesions ≤ 5 cm.

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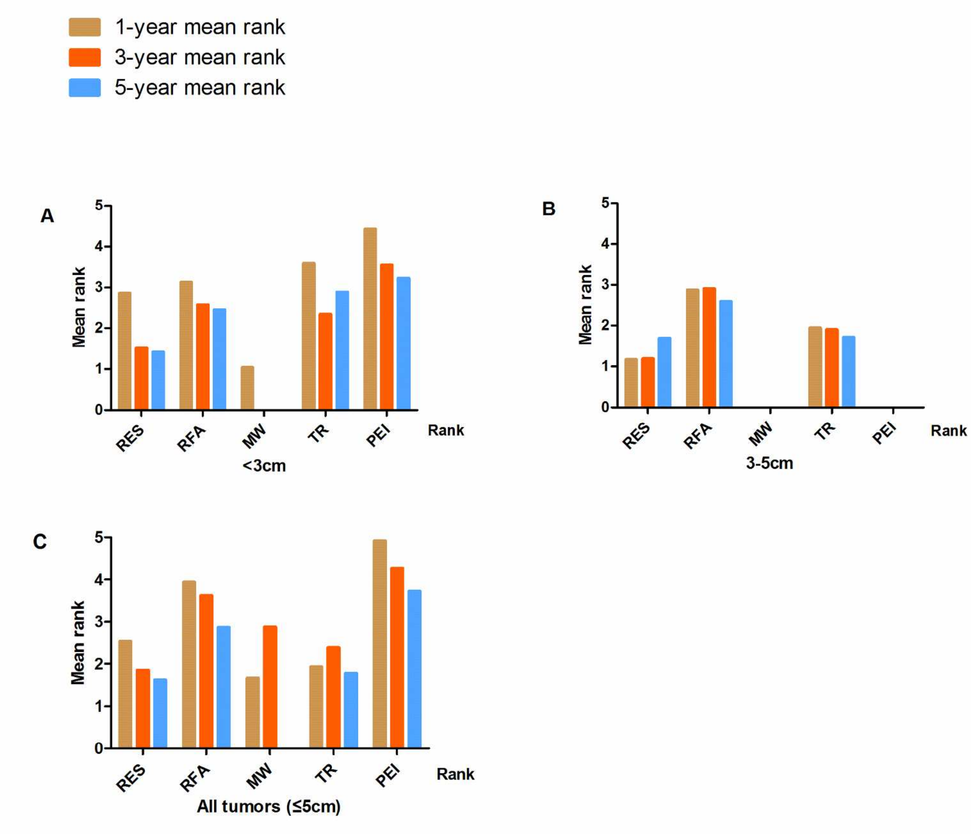


Figure 4 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in RCTs
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

193x165mm (300 x 300 DPI)

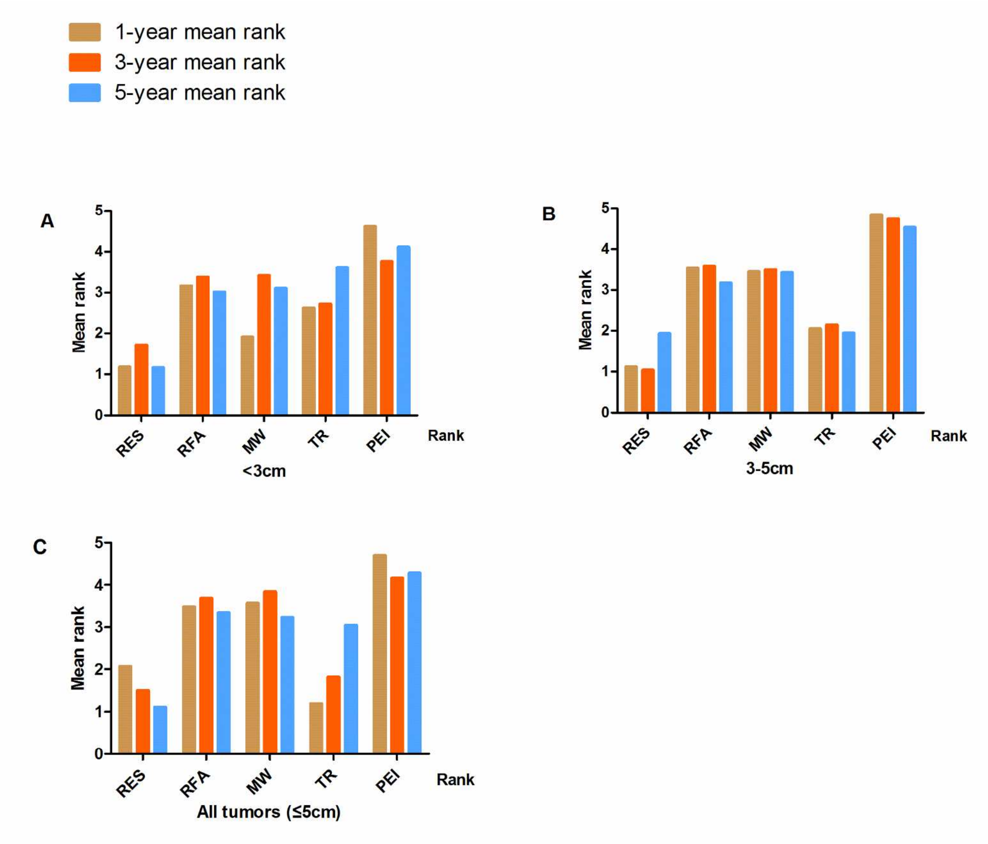


Figure 5 Treatment ranks for 1-year, 3-year and 5-year survival rates, according to lesion size in all studies.
A Lesions < 3 cm
B Lesions 3-5 cm
C Lesions ≤ 5 cm (full sample).

193x165mm (300 x 300 DPI)

Text S1.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and*	11,12

		• *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the	17

	authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Text S2.

Search strategy:

Pubmed (1950-present)

1. ("TACE" OR "transarterial chemoembolization")
2. ("RFA" OR "radiofrequency ablation" OR "RF ablation" OR "radiofrequency thermal ablation" OR "RTA")
3. (PEI OR "ethanol injection" OR "ethanol ablation" OR "alcohol ablation")
4. ("microwave ablation" OR "microwave thermal ablation" OR MWA)
5. (liver OR hepato*)
6. (neoplas* OR cancer OR tumor OR tumour OR carcinoma OR oncolog*)
7. 1 OR 2 OR 3 OR 4
8. 5 AND 6 AND 7
9. "Ablation Techniques"[Mesh]
10. "Embolization"[Mesh]
11. "Liver Neoplasms"[Mesh]
12. 9 OR 10
13. 12 AND 11
14. 8 OR 13
15. (resection OR surgery OR hepatectomy)
16. (ablation OR injection OR embolization)
17. 5 AND 6 AND 15 AND 16
18. "Hepatectomy"[Mesh]
19. 12 AND 18 AND 11
20. 17 OR 19

21. 14 OR 20

Embase(1980-present)

1. ' TACE':ab,ti
2. ' transarterial chemoembolization':ab,ti
3. 1 OR 2
4. 'rfa':ab,ti
5. 'radiofrequency ablation':ab,ti
6. 'rf ablation':ab,ti
7. 'radiofrequency thermal ablation':ab,ti
8. 'rta':ab,ti
9. 4 OR 5 OR 6 OR 7 OR 8
10. 'PEI':ab,ti
11. ' ethanol injection ':ab,ti
12. ' ethanol ablation ':ab,ti
13. ' alcohol ablation ':ab,ti
14. 10 OR 11 OR 12 OR 13
15. ' microwave ablation ':ab,ti
16. ' microwave thermal ablation ':ab,ti
17. ' MWA ':ab,ti
18. 15 OR 16 OR 17
19. ' liver':ab,ti
20. ' hepato*':ab,ti
21. 19 OR 20
22. ' neoplas*':ab,ti
23. ' cancer ':ab,ti
24. ' tumor ':ab,ti
25. ' tumour ':ab,ti
26. ' carcinoma ':ab,ti
27. ' oncolog*':ab,ti

28. 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. 3 OR 9 OR 14 OR 18
30. 21 AND 28 AND 29
31. ' resection':ab,ti
32. ' surgery':ab,ti
33. ' hepatectomy':ab,ti
34. 31 OR 32 OR 33
35. ' ablation':ab,ti
36. ' injection':ab,ti
37. ' embolization':ab,ti
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Scoups

1. TITLE-ABS-KEY (“TACE”)
2. TITLE-ABS-KEY (“transarterial chemoembolization”)
3. 1 OR 2
4. TITLE-ABS-KEY ("RFA")
5. TITLE-ABS-KEY (“radiofrequency ablation”)
6. TITLE-ABS-KEY ("RF ablation")
7. TITLE-ABS-KEY ("radiofrequency thermal ablation")
8. TITLE-ABS-KEY ("RTA")
9. 4 OR 5 OR 6 OR 7 OR8
10. TITLE-ABS-KEY (“PEI”)
11. TITLE-ABS-KEY (“ethanol injection”)
12. TITLE-ABS-KEY (“ethanol ablation”)
13. TITLE-ABS-KEY (“alcohol ablation”)
14. 10 OR 11 OR 12 OR 13
15. TITLE-ABS-KEY ("microwave ablation")

16. TITLE-ABS-KEY ("microwave thermal ablation ")
17. TITLE-ABS-KEY ("MWA")
18. 15 OR 16 OR 17
19. TITLE-ABS-KEY ("liver ")
20. TITLE-ABS-KEY ("hepato*")
21. 19 OR 20
22. TITLE-ABS-KEY ("neoplas*")
23. TITLE-ABS-KEY ("cancer")
24. TITLE-ABS-KEY ("tumor")
25. TITLE-ABS-KEY ("tumour")
26. TITLE-ABS-KEY ("carcinoma")
27. TITLE-ABS-KEY ("oncolog*")
28. 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. 3 OR 9 OR 14 OR 18
30. 29 AND 21 AND 28
31. TITLE-ABS-KEY ("resection")
32. TITLE-ABS-KEY ("surgery")
33. TITLE-ABS-KEY ("hepatectomy")
34. 31 OR 32 OR 33
35. TITLE-ABS-KEY ("ablation")
36. TITLE-ABS-KEY ("injection")
37. TITLE-ABS-KEY ("embolization")
38. 35 OR 36 OR 37
39. 34 AND 38 AND 21 AND 28
40. 30 OR 39

Web of science

1. TS=(ablation)
2. TS=(embolization)
3. 1 OR 2

4. TS=(hepatectomy)
5. TS=(liver neoplasms)
6. 3 AND 4 AND 5
7. TI=(resection)
8. TI=(surgery)
9. TI=(hepatectomy)
10. 7 OR 8 OR 9
11. TI=(ablation)
12. TI=(injection)
13. TI=(embolization)
14. 11 OR 12 OR 13
15. TI=(liver)
16. TI=(hepato*)
17. 15 OR 16
18. TI=(neoplas*)
19. TI=(cancer)
20. TI=(tumor)
21. TI=(tumour)
22. TI=(carcinoma)
23. TI=(oncolog*)
24. 18 OR 19 OR 20 OR 21 OR 22 OR 23
25. 10 AND 14 AND 17 AND 24
26. 3 AND 5
27. TI=(TACE)
28. TI=("transarterial chemoembolization")
29. 27 OR 28
30. TI=(RFA)
31. TI=("radiofrequency ablation")
32. TI=("RF ablation")
33. TI=("radiofrequency thermal ablation")
34. TI=(RTA)

35. 30 OR 31 OR 32 OR 33 OR 34
36. TI=(PEI)
37. TI=("ethanol injection")
38. TI=("ethanol ablation")
39. TI=("alcohol ablation")
40. 36 OR 37 OR 38 OR 39
41. TI=("microwave ablation")
42. TI=("microwave thermal ablation")
43. TI=(MWA)
44. 41 OR 42 OR 43
45. 29 OR 35 OR 40 OR 44
46. 46 AND 17 AND 24
47. 6 OR 25 OR 26 OR 46

Table S1.
Summary of the studies included in the network meta-analysis.

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
Zhang 2002 [23]	Prospective cohort	China	HCC	0.3-2	RFA	15(15)	13/2	61.8 (38-78)	4.1 (2.4-6.0)	NA	0.80(1y)	0.80(1y)	NA
					TR	15(15)	12/3	57.8 (39-72)	4.6 (2.3-7.1)	NA	1.00(1y)	1.00 (1y)	NA
Lencioni 2003 [24]	RCT	Italy	HCC	1.9±0.8	RFA	52(69)	36/16	67±6 (52-78)	2.8±0.6	1.00(1y)	NA	1.00(1y)	15 pain and 10 fever
					PEI	50(73)	30/20	69±7.4 (40-82)	2.8±0.8	0.96(1y)	NA	0.96(1y)	13 pain and 5 fever
Lin 2004 [25]	RCT	China	HCC	2±0.9	RFA	52(69)	35/17	62±11	2.9±0.8	0.76(3y)	NA	0.35(3y)	1 transient pleural effusion

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					PEI	52(67)	34/18	59±10	2.8±0.8	0.66(3y)	NA	0.17(3y)	1 pain
Vivarelli 2004 [26]	Retrospective cohort	Italy	HCC	2.4	RES	79(92)	57/22	65.2±8.2 (43-81)	≤3/3.1-5 (21/58)	0.81(3y)	0.59(3y)	0.65(3y)	NA
					RFA	79(112)	67/12	67.8±8.7 (41-88)	≤3/3.1-5 (22/57)	0.50(3y)	0.25(3y)	0.33(3y)	NA
Cho 2005 [27]	Retrospective cohort	Korea	HCC	0.1-3	RES	61	48/13	57	3.4±1.0	NA	0.77(3y)	0.77(3y)	2 bleeding, 1 intraabdominal abscess, 1 wound infection
					RFA	99	76/23	58	3.1±0.8	NA	0.80(3y)	0.80(3y)	1 chest wall metastasis, 1 cholecystitis, 1 iatrogenic burn, 1 ileus, 1 hepatic infarction
Huang 2005 [29]	RCT	China	HCC	1-4.9	RES	38(42)	27/11	59±11.4	≤2/2.1-3 (24/14)	0.82	NA	0.82	NA
					PEI	38(46)	19/19	63±10.9	≤2/2.1-3 (21/17)	0.45	NA	0.45	NA
Hong 2005 [28]	Retrospective cohort	Korea	HCC	2.9(0.4-4.6)	RES	93	69/24	49.2±9.9	2.5±0.8	0.84(3y)	NA	0.84(3y)	NA
					RFA	55	41/14	59.1±9.6	2.4±0.6	0.73(3y)	NA	0.73(3y)	NA
Lin 2005 [30]	RCT	China	HCC	2.3±1	RFA	62(78)	40/22	61±10	2.5±1	0.74(3y)	NA	0.74(3y)	2 haemothorax, 1 gastric bleeding and perforation
					PEI	62(76)	39/23	60±8	2.3±0.8	0.60(3y)	NA	0.60(3y)	1 pain
Lu 2005 [31]	Retrospective cohort	China	HCC	2.1±1.1	RFA	53(72)	43/10	54.5±11.7 (24-74)	2.6±1.2 (1.0-6.1)	0.38(3y)	NA	0.38(3y)	2 skin burn, 1 puncture wound infection
					MWA	49(98)	44/5	50.1±13.7 (24-74)	2.5±1.2 (0.9-7.2)	0.51(3y)	NA	0.51(3y)	2 puncture wounds, 2 subcapsular hematoma

Study Year	Design style	Countr ,	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Montorsi 2005 [32]	Prospective cohort	Italy	HCC	2.1	RES	40	33/7	67 ±9	<5cm	NA	NA	0.73(3y)	NA
					RFA	58	43/15	67 ±6		NA	NA	0.60(3y)	NA
Shiina 2005 [33]	RCT	Japan	HCC	3.1(0.6-4.3)	RFA	118(184)	79/39	≤65/>65 (44/74)	≤2/>2 (45/73)	NA	NA	0.61(3y)	1 transient jaundice, 1 skin burn, 1 hepatic infarction, 3 neoplastic seeding
					PEI	114(188)	87/27	≤65/>65 (41/73)	≤2/>2 (57/57)	NA	NA	0.45(3y)	1 abscess2 neoplastic seeding
Chen 2006 [34]	RCT	China	HCC	2.4 ±1	RES	90	75/15	49.4 ±10.9	≤3/3.1-5 (42/48)	0.53	NA	0.53	2 liver failure, 2 gastrointestinal bleeding, 27 ascites
					RFA	71	56/15	51.9 ±11.2	≤3/3.1-5 (37/34)	0.58	NA	0.58	3 skin burn
Lu 2006 [35]	RCT	China	Early HCC	1.8	RES	54(56)	37/17	49 ±14	3.2 ±1.0	NA	NA	0.86 (3y)	3 wound infection, 1 gastrointestinal bleeding
					RFA	51(57)	42/9	55 ±13	2.7 ±1.0	NA	NA	0.87 (3y)	1 peritoneal bleeding, 1 neoplastic seeding
Cho 2007 [36]	Retrospective cohort	Korea	HCC	5.7	RES	130(145)	103/27	56.3 ±8.8	≤2/2.1-3 (43/87)	0.66	NA	0.66	NA
					PEI	249(275)	181/68	57.7 ±9.7	≤2/2.1-3 (169/80)	0.49	NA	0.49	NA
Gao 2007 [37]	Retrospective cohort	China	HCC	4.6	RES	34(37)	28/6	51.5 (38-67)	2.58 ±0.41	0.76	NA	0.76	12 fever, 5 ascites
					RFA	53(84)	41/12	57.1 (31-81)	2.45 ±0.37	0.62	NA	0.62	2 bleeding, 1 fistula, 1 wound infection, 6 fever, 9 ascites
Lupo 2007 [38]	Retrospective cohort	Italy	HCC	2.6	RES	42	33/9	67(28-80)	4.0(3-5)	NA	0.43	0.43	2 urine infection, 1 bilioma, 1 pleural effusion, 1 renal failure, 1 intra-abdominal bleeding

Study Year	Design style	Countr ,	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					RFA	60	47/13	68(42-85)	3.65(3-5)	NA	0.32	0.32	2 liver failure, 1 hepatic abscess, 2 pleural effusion, 1 cutaneous metastasis
Zhou 2007 [39]	Retrospective cohort	China	HCC	0.5-5.9	RES	40(42)	35/5	53±13	≤2/2.1-5 (7/33)	NA	NA	0.75	NA
					RFA	47(54)	37/10	57±14	≤2/2.1-5 (8/39)	NA	NA	0.19	NA
Abu-Hilal 2008 [40]	Retrospective cohort	Italy and China	Early HCC	3.6	RES	34	26/8	67	3.8(1.3-5)	NA	0.56	0.56	3 hepatic failure
					RFA	34	27/7	65	3(2-5)	NA	0.56	0.56	1 artero-portal fistula
Brunello 2008 [41]	RCT	Italy	Early HCC	2.2	RFA	70(89)	49/20	70.3±8.1	1.27±0.54	0.60(3y)	NA	0.60(3y)	1 haemoperitoneum 1 right haemothorax
					PEI	69(88)	43/27	69.0±7.7	1.27±0.57	0.58(3y)	NA	0.58(3y)	1 haemoperitoneum 1 death
Guglielmi 2008 [42]	Retrospective cohort	Italy	HCC	2.3	RES	91(113)	73/18	≤65/>65 (47/44)	≤3/3.1-6 (31/60)	0.55	0.43	0.48	33 postoperative complications
					RFA	109(153)	88/21	≤65/>65 (38/71)	≤3/3.1-6 (32/77)	0.28	0.14	0.20	11 postoperative complications
Hiraoka 2008 [43]	Retrospective cohort	Japan	HCC	2.5	RES	59	44/15	62.4±10.6	2.27±0.55	0.59	NA	0.59	1 death, 2 abscess
					RFA	105	76/29	69.4±9.1	1.98±0.52	0.59	NA	0.59	1 biloma, 2 dermatitis
Bu 2009 [49]	Retrospective cohort	China	HCC	2.9(0.5-6)	RES	42(46)	36/6	53.93±10.74	≤3/3.1-5 (14/28)	0.57	0.46	0.50	1 postoperative hemorrhage, 3 pleural effusions, 2 subdiaphragmatic effusion

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	46(54)	40/6	55.89±7.37	≤3/3.1-5 (20/26)	0.50	0.31	0.37	4 pleural effusions, 1 postoperative hemorrhage, 1 skin burn
Ohmoto 2009 [44]	Retrospective cohort	Japan	HCC	2.8±2	RFA	34(37)	25/9	67 (44-78)	1.6 (0.7-2.0)	0.71	NA	0.71	2 pain, 4 fever, 1 bile duct injury, 1 pleural effusion, 1 skin burns, 1 vagovagal reflex
					MWA	49(56)	41/8	64 (38-75)	1.7 (0.8-2.0)	0.37	NA	0.37	11 pain, 17 fever, 9 bile duct injury, 8 pleural effusion, 5 ascites, 4 skin burns, 2 vagovagal reflex, 2 abscess, 2 intraperitoneal bleeding, 1 hepatic infarction, 1 portal thrombus, 1 biliary peritonitis
Sakaguchi 2009 [45]	Retrospective cohort	Japan	HCC	0.1-5	Laparoscopic /thoracoscopic RFA	249	169/80	65.6±8.9	2.48±0.89	0.57	NA	0.57	1 frequent premature ventricular contractions, 1 liver decompensation
					Laparoscopic /thoracoscopic MWA	142	107/35	64.9±7.8	2.28±0.74	0.63	NA	0.63	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Santambrogio 2009 [46]	Prospective cohort	Italy	HCC	3.2	RES	78	55/23	68±8	2.87±1.21	0.54	NA	0.54	15 extra-hepatic complications

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					Laparoscopic RFA	74	59/15	68±7	2.63±1.07	0.41	NA	0.41	14 extra-hepatic complications
Shibata 2009 [47]	RCT	Japan	HCC	2.5±1.2	RFA	43(44)	33/10	69.8±8 (44-87)	1.6±0.5 (0.8-2.6)	0.84(3y)	NA	0.84(3y)	1 pseudoaneurysm
					TR	46(49)	31/15	67.2±8.9 (45-83)	1.7±0.6 (0.9-3.0)	0.85(3y)	NA	0.85(3y)	1 hepatic infarction
Ueno 2009 [48]	Retrospective cohort	Japan	HCC	3(0.3-7.9)	RES	123(136)	82/41	67(28-85)	2.7±0.1	0.81	0.72	0.80	NA
					RFA	155(209)	100/55	66(40-79)	2.0±0.1	0.38	0.78	0.63	NA
Guo 2010 [50]	Retrospective cohort	China	HCC	2.5	RES	73(155)	57/16	50.0 (17.0-68.0)	≤3/3.1-5 (30/43)	0.27	0.47	0.44	1 postoperative hemorrhage, 5 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	86(211)	63/23	52.5 (26.0-80.0)	≤3/3.1-5 (42/44)	0.33	0.16	0.21	1 postoperative hemorrhage, 1 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Huang 2010 [51]	RCT	China	HCC	3.87	RES	115(144)	85/30	55.91±12.68	≤3/3.1-5 (45/44)	0.82	0.73	0.76	1 hepatic failure, 13 ascites, 5 effusion, 9 bile leakage, 2 postoperative bleeding, 2 gastrointestinal bleeding
					RFA	115(147)	79/36	56.57±14.30	≤3/3.1-5 (57/27)	0.61	0.52	0.55	1 gastric perforation, 2 hemorrhage, 1 malignant seeding, 1 hepatic infarction
Kagawa 2010 [52]	Retrospective cohort	Japan	Early HCC	4.2	RES	55(69)	40/15	66.1±8.4	≤2/2.1-5 (9/46)	0.42	NA	0.42	2 deaths, 1 liver failure, 1 pleural effusion, 1 pneumonia, 2 biliary leakage

Study Year	Design style	Countr y	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					TR	62(79)	39/23	67.5±8.4	≤2/2.1-5 (19/43)	0.29	NA	0.29	1 duodenal perforation, 1 hemothorax
Morimoto 2010 [53]	RCT	Japan	HCC	2.7	RFA	18(25)	12/6	73 (48-84)	3.7±0.6	NA	0.78(3y)	0.78(3y)	5 pain, 2 pleural effusion
					TR	19(21)	15/4	70 (57-78)	3.6±0.7	NA	0.95(3y)	0.95(3y)	1 pain, 1 pleural effusion
Azab 2011 [54]	RCT	Egypt	HCC	1.5	RFA	30(33)	75/15	46-77	<5cm	NA	NA	0.90	5 superficial burn, 17 transient pain, 3 portal vein thrombosis, 7 fever, 1 ascites
					PEI	30(32)				NA	NA	0.83	2 portal vein thrombosis, 3 fever, 3 ascites
Giorgio 2011 [55]	RCT	Italy	HCC	1.8	RFA	142	105/37	70±2 (68-74)	2.34±0.45 (1.1-3)	0.70	NA	0.70	1 major complication
					PEI	143	102/41	72±6 (68-79)	2.27±0.48 (1.3-2.9)	0.68	NA	0.68	3 major complication
Hung 2011 [56]	Retrospective cohort	China	Early HCC	3.5±2	RES	229	184/45	60.07±12.56	2.88±1.06	0.77	NA	0.77	NA
					RFA	190	121/69	67.42±11.45	2.37±0.92	0.67	NA	0.67	NA
Nishikawa 2011 [57]	Retrospective cohort	Japan	HCC	3.3	RES	69	50/19	67.4±9.7	2.68±0.49	0.74	NA	0.74	2 bile leakage, 2 ascites, 1 acute respiratory distress syndrome, 1 gastrointestinal bleeding
					RFA	162	95/67	68.4±8.7	1.99±0.62	0.63	NA	0.63	1 biloma, 1 ascites, 1 intra-abdominal bleeding
Yun 2011 [58]	Retrospect	Korea	HCC	3.5(0.1-9.	RES	215	171/44	51.7±9.7	2.1±0.5	0.94	NA	0.94	NA

Study Year	Design style	Countr	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
	ive cohort			1)	RFA	255	197/58	57.0±9.9	2.1±0.5	0.87	NA	0.87	NA
Zhang 2011 [59]	Retrospective cohort	China	HCC	0.5-3.5	RES	103(117)	78/25	56.4±15.2	<5cm	NA	NA	0.35(3y)	12 wound infection, 5 postoperative hemorrhage, 2 hepatic failure, 15 pleural effusions, 6 pleural effusions
					RFA	85(106)	62/23	58.5±12.9	<5cm	NA	NA	0.39(3y)	2 gallbladder cardiac reflex, 4 postoperative hemorrhage, 3 pleural effusions
Feng 2012 [61]	RCT	China	HCC	3	RES	84(116)	75/9	47 (18-76)	2.6±0.8	0.62(3y)	NA	0.62(3y)	7 pleural effusion, 3 pneumonia, 1 effusion plus infection, 3 wound infection or dehiscence, 1 biliary fistula, 2 abdominal bleeding, 1 pneumothorax or hemothorax
					RFA	84(120)	79/5	51 (24-83)	2.4±0.6	0.55(3y)	NA	0.55(3y)	5 pleural effusion, 1 liver abscess, 2 abdominal bleeding
Peng 2012 [62]	Retrospective cohort	China	Recurrent HCC	4.9	RES	74	65/9	51.5±12.1 (24-75)	1.1±0.5 (0.8-2.0)	0.62	NA	0.62	1 liver failure, 2 gastrointestinal bleeding, 1 peritoneal bleeding, 1 intestinal obstruction, 1 spontaneous bacterial peritonitis, 1 persistent jaundice, 31 ascites

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	71	63/8	53.1±12.1 (28-74)	1.2±0.6 (0.9-2.0)	0.72	NA	0.72	1 gastrointestinal bleeding, 1 persistent jaundice, 12 ascites
Peng 2012 [63]	RCT	China	Recurrent HCC	3.3±1.8	RFA	70(76)	55/15	55.1±9.5 (22-75)	≤3/3.1-5 (46/24)	NA	0.17	0.36	1 persistent jaundice, 1 ascites, 22 fever, 45 pain, 4 vomiting
					TR	69(74)	59/9	57.5±10.0 (19-75)	≤3/3.1-5 (41/28)	NA	0.39	0.46	1 liver failure, 1 ascites, 27 fever, 50 pain, 42 vomiting
Signoriello 2012 [64]	Retrospective cohort	Italy	HCC	0.1-9	RES	34(44)	30/4	62±7	≤3/3.1-5/>5.1 (13/9/4)	NA	NA	0.29	NA
					RFA	50(74)	40/10	68±7	≤3/3.1-5/>5.1 (24/11/7)	NA	NA	0.15	NA
					PEI	256(349)	188/68	67±8	≤3/3.1-5/>5.1 (143/43/12)	NA	NA	0.20	NA
a. Wang 2012 [65]	Retrospective cohort	China	Early HCC	2.5	RES	52	38/14	≤60 (35)	NA	NA	NA	0.92	NA
					RFA	91	60/31	≤60 (40)		NA	NA	0.73	NA
b. Wang 2012 [65]	Retrospective cohort	China	Early HCC	2.5	RES	208	168/40	≤60 (113)	≤2/2.1-5 (6/202)	NA	NA	0.77	NA
					RFA	254	161/93	≤60 (85)	≤2/2.1-5 (60/194)	NA	NA	0.57	NA
Desiderio 2013 [66]	Retrospective cohort	Italy	HCC	4.3(2.3-5)	RES	52(94)	37/15	65.6±4.8	≤3	0.46	NA	0.46	2 hepatic failure, 1 biliary fistula, 2 hemoperitoneum, 9 ascites
					RFA	44(81)	35/9	64.4±6.5		0.36	NA	0.36	6 pain, 7 fever

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Ding 2013 [67]	Retrospective cohort	China	HCC	2.3±1.3	RFA	85(98)	68/17	58.64±8.52 (40-77)	2.38±0.81 (1.0-4.8)	0.82(3y)	NA	0.82(3y)	1 frequent premature ventricular contractions, 1 liver decompensation
					MWA	113(131)	85/28	59.06±11.68 (30-86)	2.55±0.89 (0.8-5.0)	0.78(3y)	NA	0.78(3y)	1 breath holding and incomplete intestinal obstruction, 2 liver decompensation
Guo 2013 [68]	Retrospective cohort	China	HCC	2.7	RES	102(129)	94/8	51.5(18-75)	≤3/3.1-5 (75/27)	NA	NA	0.63	5 postoperative hemorrhage, 3 bile leak, 4 abscess, 3 infected ascites, 1 liver failure, 4 pleural effusion
					RFA	94(125)	78/16	56(19-75)	≤3/3.1-5 (62/32)	NA	NA	0.50	1 postoperative hemorrhage, 2 bile leak, 1 abscess, 1 infected ascites, 3 pleural effusion
Hasegawa 2013 [69]	Retrospective cohort	Japan	HCC	2.2	RES	5361(6461)	3967/1394	66 (48-77)	2.3 (1.2-3)	0.71	NA	0.71	NA
					RFA	5548(7412)	3569/1979	69 (52-80)	2 (1-3)	0.61	NA	0.61	NA
					PEI	2059(2836)	1303/756	69 (52-80)	1.7 (1-3)	0.56	NA	0.56	NA
Iida 2013 [70]	Retrospective cohort	Japan	HCC	0.1-7.5	Laparoscopic RFA	18(27)	NA	73.5±4.0	2.1±0.5	0.78	NA	0.78	1 abscess

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated)			Complication
										<3cm	3-5cm	All	
					Laparoscopic MWA	40(56)		70.1 ±6.6	2.0 ±0.9	0.78	NA	0.78	1 abscess
Imai 2013 [71]	Retrospective cohort	Japan	HCC	4.1	RES	101	75/26	63.3 ±9.7	2.14 ±0.55	0.87	NA	0.87	NA
					RFA	82	46/36	67.6 ±8.5	1.87 ±0.50	0.60	NA	0.60	NA
Kim 2013 [72]	Retrospective cohort	Korea	Early HCC	0.1-4.2	RES	47	36/11	58.8 ±10.7	3.66 ±0.76	NA	0.85(3y)	0.85(3y)	2 pleural effusion, 2 pneumonia, 1 hepatic failure, 1 hepatic abscess, 1 mechanical ileus
					TR	37	31/6	61.7 ±11.1	3.46 ±0.75	NA	0.78(3y)	0.78(3y)	1 bile duct dilatation
Lai 2013 [73]	Retrospective cohort	China	HCC	2.9 ±1.5	RES	80	55/25	60.8 ±9.9	2.9 ±1.1	0.71	NA	0.71	NA
					RFA	31	19/12	63.1 ±12.8	1.8 ±0.6	0.84	NA	0.84	NA
Lin 2013 [74]	Retrospective cohort	China	Early HCC	3.4	RFA	658	393/265	64.7 ±10.5	2.4 ±1.1 (0.8-9.5)	0.60	0.50	0.55	NA
					PEI	378	243/135	63.5 ±12.1	2.0 ±0.9 (0.4-7.0)	0.50	0.28	0.40	NA
Peng 2013 [75]	RCT	China	HCC	0.6-5.2	RFA	95(133)	71/24	55.3 ±13.3	3.39 ±1.35	NA	0.59(3y)	0.59(3y)	51 pain, 26 fever, 29 vomiting, 4 ascites, 2 pleural effusion, 1 skin burn, 1 abdominal infection, 1 small intestinal obstruction
					TR	94(137)	75/19	53.3 ±11	3.47 ±1.44	NA	0.67(3y)	0.67(3y)	57 pain, 33 fever, 40 vomiting, 5 ascites, 3 pleural effusion, 1 skin burn, 1 bile duct stenosis, 1 gastric hemorrhage

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Tohme 2013 [76]	Retrospective cohort	America	Early HCC	2.4	RES	50(62)	31/19	66.3±1	3.07±1.17	0.48	NA	0.48	3 pleural effusion, 1 pneumonia, 1 myocardial infarction, 2 biloma, 2 ileus, 1 ascites, 1 hyperbilirubinaemia >6, 1 renal insufficiency, 2 encephalopathy
					RFA	60(75)	38/22	65.6±12	2.36±0.94	0.35	NA	0.35	1 oesophagitis, 3 encephalopathy, 1 cholangitis, 2 ascites, 1 renal insufficiency, 1 pneumonia
Wong 2013 [77]	Retrospective cohort	China	Early HCC	0.1-5	RES	46	30/16	55.1±12	2.1±0.6	0.85	NA	0.85	2 fever, 1 increased serum alanine aminotransferase level, 2 atelectasis, 2 biloma
					RFA	36	18/18	63.5±13	1.9±0.6	0.72	NA	0.72	None
Zhang 2013 [78]	Retrospective cohort	China	HCC	2.2±1	RFA	78(97)	64/14	54±10.5 (30-80)	≤3/3.1-5 (47/31)	0.43	0.39	0.41	1 persistent jaundice, 1 biliary fistula
					MWA	77(105)	67/10	54±9.5 (26-76)	≤3/3.1-5 (36/41)	0.58	0.29	0.39	1 hemothorax and intrahepatic hematoma, 1 peritoneal hemorrhage
Abdelaziz 2014 [79]	RCT	Egypt	Early HCC	2.3	RFA	45(52)	31/14	56.8±7.3	2.95±1.03	0.68(1y)	NA	0.68(1y)	2 subcapsular hematoma, 1 thigh burn, 2 pleural effusion
					MWA	66(76)	48/18	53.6±5	2.9±0.97	0.96(1y)	NA	0.96(1y)	1 subcapsular hematoma, 1 abdominal wall skin burn
Shi 2014 [80]	Retrospective cohort	China	HCC	3.8	RES	107(126)	87/20	54.5±9.9	≤3/3.1-5 (37/54)	0.73	0.57	0.60	NA

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					MWA	117(143)	93/24	56.6±9.2	≤3/3.1-5 (40/56)	0.65	0.52	0.52	NA
Yang 2014 [81]	Retrospective cohort	Korea	HCC	0.1-7	RES	52	38/14	55.7±10.6	≤2/2.1-5 (21/31)	0.94	NA	0.94	2 pneumonia, 1 wound infection, 1 biliary anastomotic leak, 1 portal vein thrombosis, 1 nausea, 1 delirium, 4 ascites
					RFA	79	59/20	57.2±9.2	≤2/2.1-5 (36/43)	0.86	NA	0.86	1 vomiting, 1 ascites, 6 abdominal pain, 2 nausea, 1 sinus bradycardia
Zhang 2014 [82]	Retrospective cohort	China	Recurrent HCC	2.7	RES	27(29)	25/2	47±13	3.2±1.0	NA	NA	0.63	NA
					MWA	39(46)	37/2	52±13	2.7±1.1	NA	NA	0.62	NA
Pompili 2015 [83]	Retrospective cohort	Italy	Early HCC	2.8	RFA	136	75/61	68 (41-85)	1.8 (1-2)	0.63	NA	0.63	2 ascites, 1 pleural effusion, 1 hemobilia
					PEI	108	90/18	68.5 (34-86)	1.95 (0.8-2)	0.65	NA	0.65	1 hemobilia, 1 portal vein thrombosis
Xu 2015 [84]	RCT	China	HCC	0.1-3	Laparoscopic RES	45	34/11	58.3±3.1 (26-78)	3.6±0.7 (1-5)	NA	0.38(3y)	0.38(3y)	3 bile leakage, 3 pleural effusion, 2 postoperative hemorrhage
					MWA	45	32/13	57.9±3.4 (27-76)	3.8±0.9 (2-5)	NA	0.33(3y)	0.33(3y)	1 bile leakage, 1 pleural effusion, 1 postoperative hemorrhage

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Agcaoglu O 2013[96]	Prospective cohort	America	HCC	1.7	RES	94	50/44	61.7±1.2	3.7±0.2	NA	0.53	0.53	2 pulmonary,2 biliary,2 wound-related,1 intestinal,1 hemorrhagic,2 cardiac , and 1 renal
					RFA	295	196/99	63.4 ±0.7	3.4±0.1	NA	0.2	0.2	3 bleeding,2 liver abscess,5 pulmonary,3 renal
Zhou Z 2014[93]	Retrospective cohort	China	HCC	5	RES	21	15/6	42.2±7.6	1.7±0.3	0.81	NA	0.81	1 intraperitoneal hemorrhage
					RFA	31	20/11	46.7±9.8	1.7±0.4	0.81	NA	0.81	2 pleural effusion;2 fever;1 pneumonia;1 biloma
Kim JM 2014[95]	Retrospective cohort	Korea	HCC	2.8	RES	66	48/18	58.	2.1(0.8-3.0)	0.89	NA	0.89	NA
					RFA	67	52/15	59	1.8 (1.0-2.9)	0.49	NA	0.49	NA
Ko S 2014[94]	Retrospective cohort	China	HCC	5	RES	12	9/3	71.6±4.3	2.9±1.4	NA	NA	0.67	NA
					RFA	17	9/8	57.3±3.6	2.3±1.1	NA	NA	0.35	NA
Kang TW 2015[92]	Retrospective cohort	Korea	HCC	5	RES	142	107/35	53(28-74)	2(1.1–3.0)	0.90	NA	0.90	1 intra-abdominal abscess,3 wound problem,1 abdominal bleeding,1 intestinal obstruction

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
					RFA	438	337/101	58(30-80)	1.9(1.1–3.0)	0.85	NA	0.85	3 tumor seeding,2 biloma,2 hepatic abscess,1 bile duct stricture,1 hepatic infarction
Lee YH 2015 [91]	Retrospective cohort	China	HCC	3.63	RES	330	261/69	61 ±12	<5	NA	NA	0.76	NA
					RFA	369	244/125	66 ± 11	<5	NA	NA	0.66	NA
Liu PH 2016 [87]	Prospective cohort	China	HCC	3.7	RES	109	78/31	60 ±13	<2	NA	0.81	0.81	NA
					RFA	128	84/44	64 ±12	<2	NA	0.76	0.76	NA
Hof J 2016 [89]	Retrospective cohort	Netherlands	HCC	3.2	RES	261	151/110	63.4	<5	0.69	NA	0.69	NA
					RFA	75	55/20	65.7	<5	NA	0.33(3y)	0.33(3y)	NA
Lee HW 2018 [85]	RCT	Korea	HCC	5	RES	29	23/6	55.6 ±7.9	<5	NA	0.97(3y)	0.97(3y)	7 pleural effusion
					RFA	34	24/10	56.1 ±7.4	<5	NA	0.97(3y)	0.97(3y)	3 pain

Study Year	Design style	Country	Disease type	Follow-up (year)	Treatment style	Group n (Tumor n)	Male/ Female	Age	Tumor size, cm	5-year Survival rates (unless stated) <3cm	3-5cm	All	Complication
Li W 2017 [86]	Retrospective cohort	China	HCC	5	RES	220(239)	37/183	61.8 (40-73)	2.1 ±0.5	0.75	NA	0.75	64 complications
					MWA	60(61)	14/46	65(45-71)	2.0 ±0.5	0.67	NA	0.67	13 complications
Vogl TJ 2015 [90]	Retrospective cohort	Germany	HCC	5	RFA	25(32)	19/6	57 ±3.5	3.2(0.8-4.5)	0.72(3y)	NA	0.72(3y)	NA
					MWA	28(36)	23/5	60 ±4.2	3.6(0.9-5)	0.79	NA	0.79(3y)	NA
Liu H 2016 [88]	RCT	China	HCC	4.7	TR	100(114)	86/14	52(31-80)	2.8(0.6-5)	0.67	NA	0.67	8 pleural effusion,5 biliary fstula,4 abdominal ascites,2 liver dysfunction,2 pneumonia,1 wound infection,1 abdominal infection
					RES	100(109)	94/6	49(30-76)	3(0.6-5)	0.84	NA	0.84	4 pleural effusion,3 liver dysfunction,3 abdominal ascites,1 abdominal bleeding

HCC: hepatocellular carcinoma;
BCLC: Barcelona Clinic Liver Cancer;
RES: resection;
RFA: radiofrequency ablation;
MWA: microwave ablation;
TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

RCT: randomized controlled trial;

NA: not available.

Table S2.
Quality assessment of included studies using GRADE framework.

Intervention/Comparator	Illustrative comparative risks* (per 1000, 95% CI)		Relative effect of survival time (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Comparator Assumed survival risk	Corresponding survival risk with intervention			
1-year OS rate					
RES/MWA	923	984 (932 to 997)	**OR 5.25 (1.15 to 23.97)**	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	947	944 (902 to 968)	OR 0.94 (0.52 to 1.71)	990 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	835	802 (674 to 889)	OR 0.80 (0.41 to 1.58)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	944	963 (906 to 1000)	OR 1.02 (0.96 to 1.09)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	932	945 (931 to 956)	OR 1.25 (0.99 to 1.60)	5006 (30 studies)	⊕⊕⊕⊕ high
RES/TR	939	904 (765 to 965)	OR 0.61 (0.21 to 1.79)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	938	802 (310 to 978)	OR 0.27 (0.03 to 2.90)	31 (1 study)	⊕⊕⊖⊖ low
3-year OS rate					

RES/MWA	712	734 (623 to 822)	OR 1.12 (0.67 to 1.87)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	736	779 (717 to 828)	OR 1.26 (0.91 to 1.73)	987 (6 studies)	⊕⊕⊖⊖ low
RES/PEI	499	536 (421 to 645)	OR 1.16 (0.73 to 1.83)	519 (3 studies)	⊕⊕⊖⊖ low
RFA/PEI	729	748 (657 to 822)	OR 1.10 (0.71 to 1.71)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	785	851 (823 to 875)	**OR 1.57 (1.28 to 1.93)**	15906 (30 studies)	⊕⊕⊕⊖ moderate
RES/TR	798	760 (618 to 860)	OR 0.80 (0.41 to 1.55)	201 (2 studies)	⊕⊕⊖⊖ low
RFA/TR	737	611 (516 to 704)	OR 0.56 (0.38 to 0.85)	454 (4 studies)	⊕⊕⊕⊖ moderate
5-year OS rate					
RES/MWA	545	607 (492 to 712)	OR 1.29 (0.81 to 2.07)	290 (2 studies)	⊕⊕⊖⊖ low
RFA/MWA	545	609 (442 to 756)	OR 1.30 (0.66 to 2.58)	687 (4 studies)	⊕⊕⊖⊖ low
RES/PEI	293	436 (334 to 545)	**OR 1.87 (1.21 to 2.90)**	519 (3 studies)	⊕⊕⊕⊖ moderate
RFA/PEI	533	496 (368 to 624)	OR 0.86 (0.51 to 1.45)	9187 (4 studies)	⊕⊕⊖⊖ low
RES/RFA	601	744 (705 to 779)	**OR 1.93 (1.59 to 2.34)**	15154 (25 studies)	⊕⊕⊕⊖ moderate

RES/TR	290	419 (251 to 607)	OR 1.76 (0.82 to 3.78)	117 (1 study)	⊕⊕⊖⊖ low
RFA/TR	464	356 (222 to 523)	OR 0.64 (0.33 to 1.27)	139 (1 study)	⊕⊕⊕⊖ moderate

The absolute and relative risk of survival with treatments*. GRADE: Grading of Recommendations, Assessment, Development and Evaluation. *The results presented in the Table S1 were built around the assumption of a consistent relative effect. The implications of this effect for populations were considered at different baseline risks. Based on the assumed risks, corresponding risks after an intervention were calculated using the meta-analytic risk ratio.

Table S3.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in RCT.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	13			11			5		
RES		2	2.86		1	1.52		1	1.42
RFA		3	3.13		3	2.58		2	2.46
MWA		1	1.04		NA	NA		NA	NA
TR		4	3.59		2	2.35		3	2.89
PEI		5	4.43		4	3.55		4	3.23
3-5cm	4			4			2		
RES		1	1.17		1	1.19		1	1.69
RFA		3	2.88		3	2.91		3	2.60
MWA		NA	NA		NA	NA		NA	NA
TR		2	1.94		2	1.90		2	1.71
PEI		NA	NA		NA	NA		NA	NA
All tumours (⩽	20			16			7		

5cm)						
RES	3	2.53	1	1.85	1	1.62
RFA	4	3.94	4	3.62	3	2.87
MWA	1	1.67	3	2.88	NA	NA
TR	2	1.93	2	2.38	2	1.78
PEI	5	4.92	5	4.27	4	3.73

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S4.

Ranking treatments of 1-, 3-year and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm in all studies.

Treatment	1-year			3-year			5-year		
	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank	Study numbers (n)	Rank	Meanrank
< 3cm	50			48			37		
RES		3	1.18		1	1.71		1	1.16
RFA		4	3.17		3	3.38		2	3.02
MWA		1	1.91		4	3.42		3	3.11
TR		2	2.63		2	2.73		4	3.61
PEI		5	4.62		5	3.76		5	4.11
3-5cm	19			18			12		
RES		1	1.12		1	1.04		1	1.93
RFA		4	3.54		4	3.58		3	3.18
MWA		3	3.45		3	3.50		4	3.43
TR		2	2.05		2	2.14		2	1.94
PEI		5	4.84		5	4.74		5	4.53

All tumours (⩽ 5cm) 72			68		50	
RES	2	2.07	1	1.50	1	1.11
RFA	3	3.48	3	3.68	4	3.34
MWA	4	3.57	4	3.84	3	3.23
TR	1	1.19	2	1.82	2	3.05
PEI	5	4.70	5	4.16	5	4.28

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection.

Table S5.

Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.97 (0.42-1.98)	0.98 (0.77-1.26)
MWA vs RES	**152 (1.44-505.80)**	NA
TR vs RES	1.08 (0.15-3.78)	0.99(0.67-1.47)
PEI vs RES	0.64 (0.18-1.61)	1.03 (0.54-1.94)
MWA vs RFA	**173.30 (1.90-537.40)**	1.42 (0.63-3.19)
TR vs RFA	1.25 (0.16-4.64)	1.00 (0.56-1.80)
PEI vs RFA	0.67 (0.28-1.35)	0.97 (0.78-1.19)
TR vs MWA	**0.15 (0-0.80)**	NA
PEI vs MWA	**0.08 (0-0.38)**	NA
PEI vs TR	1.17 (0.11-4.66)	NA
3-year OS rate for treatment vs reference		

RFA vs RES	0.75 (0.41-1.31)	0.92 (0.71-1.19)
MWA vs RES	NA	NA
TR vs RES	1.17 (0.16-4.17)	0.80(0.52-1.22)
PEI vs RES	0.58 (0.29-1.16)	1.21 (0.59-2.15)
MWA vs RFA	NA	NA
TR vs RFA	1.54 (0.25-13.43)	1.01 (0.55-1.87)
PEI vs RFA	0.79 (0.45-1.39)	0.91 (0.71-1.17)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	1.02 (0.14-3.56)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.10-2.47)	0.93 (0.62-1.37)
MWA vs RES	NA	NA
TR vs RES	0.84 (0.03-4.18)	0.88(0.69-1.12)
PEI vs RES	0.50 (0.04-2.04)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	2.87 (0.04-13.43)	NA
PEI vs RFA	0.94 (0.08-3.97)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	3.93 (0.03-19.61)	NA

Table S6.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.25 (0-1.47)	0.89 (0.45-1.77)
MWA vs RES	NA	NA

TR vs RES	1.00 (0-5.0)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.40 (0.64-11.93)	1.10 (0.78-1.55)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.24 (0-1.25)	0.70 (0.34-1.45)
MWA vs RES	NA	NA
TR vs RES	1.14 (0-6.20)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	3.98 (0.71-15.22)	1.29 (0.87-1.89)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA
5-year OS rate for treatment vs reference		
RFA vs RES	1.05 (0.03-5.33)	0.71 (0.32-1.57)
MWA vs RES	NA	NA
TR vs RES	12.87 (0.02-44.43)	NA
PEI vs RES	NA	NA
MWA vs RFA	NA	NA
TR vs RFA	7.64 (0.14-42.49)	1.93 (0.53-7.06)
PEI vs RFA	NA	NA
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	NA	NA

Table S7.

Survival rates (1-year, 3-year and 5-year) for lesion (≤5cm) treatment comparisons estimated by direct and network meta-analysis in RCT.

Intervention	OR (95%CI)	
	Network Meta-analysis	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.57 (0.27-1.08)	0.96 (0.78-1.19)
MWA vs RES	2.01 (0.47-5.70)	0.98 (0.54-1.78)
TR vs RES	1.50 (0.48-3.67)	0.99 (0.67-1.47)
PEI vs RES	**0.37 (0.13-0.82)**	1.03 (0.54-1.94)
MWA vs RFA	3.84 (0.81-11.60)	1.42 (0.63-3.19)
TR vs RFA	**2.69 (1.02-6.04)**	1.09 (0.84-1.43)
PEI vs RFA	0.65 (0.33-1.13)	0.95 (0.80-1.14)
TR vs MWA	1.09 (0.16-3.50)	NA
PEI vs MWA	**0.27 (0.05-0.84)**	NA
PEI vs TR	**0.29 (0.09-0.73)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.65 (0.31-1.29)	0.88 (0.71-1.10)
MWA vs RES	1.00 (0.16-3.30)	0.88 (0.39-1.98)
TR vs RES	0.98 (0.35-2.41)	0.80 (0.51-1.22)
PEI vs RES	0.55 (0.19-1.44)	1.12 (0.59-2.15)
MWA vs RFA	1.77 (0.22-6.24)	NA
TR vs RFA	1.56 (0.66-3.25)	1.20 (0.90-1.60)
PEI vs RFA	0.86 (0.39-1.79)	0.84 (0.66-1.07)
TR vs MWA	1.86 (0.21-7.59)	NA
PEI vs MWA	1.05 (0.12-4.56)	NA
PEI vs TR	0.64 (0.19-1.67)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.66 (0.20-1.62)	0.88 (0.65-1.18)
MWA vs RES	NA	NA

TR vs RES	1.35 (0.23-4.69)	0.80 (0.52-1.22)
PEI vs RES	0.41 (0.11-1.02)	0.55 (0.26-1.15)
MWA vs RFA	NA	NA
TR vs RFA	2.29 (0.41-7.61)	1.30 (0.70-2.41)
PEI vs RFA	0.74 (0.16-2.00)	0.97 (0.66-1.40)
TR vs MWA	NA	NA
PEI vs MWA	NA	NA
PEI vs TR	0.53 (0.06-1.90)	NA

OR: odds ratio;
RES: resection;
RFA: radiofrequency ablation;
MWA: microwave ablation;
TR: transcatheter arterial chemoembolization and radiofrequency ablation;
PEI: percutaneous ethanol injection;
NA: not available.

Table S8.
Survival rates (1-year, 3-year and 5-year) for small lesion (<3cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.94 (0.39-1.91)	1.00(0.95-1.04)
MWA vs RES	1.49 (0.44-3.85)	1.02(0.72-1.43)
TR vs RES	1.30 (0.28-3.88)	1.01(0.74-1.39)
PEI vs RES	0.63 (0.22-1.44)	1.00 (0.93-1.07)
MWA vs RFA	1.59 (0.69-3.17)	1.02 (0.85-1.23)
TR vs RFA	1.48 (0.34-4.23)	1.00(0.56-1.80)
PEI vs RFA	0.68 (0.38-1.09)	0.99 (0.93-1.06)

TR vs MWA	1.08 (0.21-7.87)	NA
PEI vs MWA	0.49 (0.18-1.10)	NA
PEI vs TR	0.69 (0.14-2.13)	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.72 (0.37-1.30)	**0.94 (0.90-0.99)**
MWA vs RES	0.73 (0.30-1.55)	0.95 (0.78-1.18)
TR vs RES	0.90 (0.31-2.10)	1.08 (0.64-1.33)
PEI vs RES	0.68 (0.30-1.39)	1.00 (0.71-1.40)
MWA vs RFA	1.02 (0.57-1.70)	1.00 (0.82-1.22)
TR vs RFA	1.31 (0.47-2.92)	1.01 (0.55-1.87)
PEI vs RFA	0.96 (0.59-1.50)	0.97 (0.90-1.03)
TR vs MWA	1.38 (0.42-3.40)	NA
PEI vs MWA	1.01 (0.47-1.95)	NA
PEI vs TR	0.90 (0.29-2.17)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.54 (0.24-1.05)	**0.85 (0.81-0.90)**
MWA vs RES	0.55 (0.19-1.25)	0.88 (0.61-1.30)
TR vs RES	**0.49 (0.16-0.18)**	0.77 (0.53-1.11)
PEI vs RES	**0.43 (0.17-0.89)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.04 (0.50-1.77)	1.02 (0.78-1.33)
TR vs RFA	0.99 (0.32-2.39)	NA
PEI vs RFA	0.82 (0.48-1.29)	**0.92 (0.85-0.99)**
TR vs MWA	1.03 (0.28-2.73)	NA
PEI vs MWA	0.86 (0.39-1.65)	NA
PEI vs TR	1.07 (0.31-2.72)	NA

Table S9.

Survival rates (1-year, 3-year and 5-year) for lesion (3-5cm) treatment comparisons estimated by direct and network meta-analysis in all studies.

Intervention	OR (95%CI)

	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	**0.12 (0-0.63)**	0.96 (0.81-1.14)
MWA vs RES	0.15 (0-1.00)	NA
TR vs RES	0.36 (0.01-2.08)	1.02 (0.55-1.88)
PEI vs RES	**0.06 (0-0.31)**	NA
MWA vs RFA	1.29 (0.32-3.60)	0.99 (0.60-1.64)
TR vs RFA	**2.99 (1.14-6.58)**	1.11 (0.80-1.54)
PEI vs RFA	0.49 (0.18-1.12)	0.89 (0.66-1.20)
TR vs MWA	3.39 (0.58-10.44)	NA
PEI vs MWA	0.55 (0.09-1.76)	NA
PEI vs TR	**0.20 (0.05-0.54)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	**0.11 (0.01-0.40)**	**0.72 (0.60-0.88)**
MWA vs RES	**0.12 (0.01-0.53)**	1.02 (0.57-1.81)
TR vs RES	0.26 (0.01-1.10)	0.92 (0.48-1.75)
PEI vs RES	**0.06 (0-0.28)**	NA
MWA vs RFA	1.15 (0.39-2.65)	0.81 (0.45-1.43)
TR vs RFA	2.38 (0.93-5.38)	1.29 (0.87-1.89)
PEI vs RFA	0.55 (0.12-1.69)	0.71 (0.50-1.00)
TR vs MWA	2.62 (0.61-7.90)	NA
PEI vs MWA	0.61 (0.08-2.26)	NA
PEI vs TR	0.28 (0.04-0.96)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	0.69 (0.04-3.16)	**0.53 (0.40-0.68)**
MWA vs RES	1.24 (0.02-4.46)	0.90 (0.48-1.69)
TR vs RES	14.31 (0.04-21.06)	NA
PEI vs RES	3.02 (0.01-2.40)	NA
MWA vs RFA	1.26 (0.19-4.04)	0.57 (0.21-1.51)
TR vs RFA	6.16 (0.27-25.58)	2.36 (0.66-8.37)
PEI vs RFA	0.86 (0.06-2.68)	**0.56 (0.37-0.84)**

TR vs MWA	11.97 (0.19-46.76)	NA
PEI vs MWA	4.15 (0.04-5.18)	NA
PEI vs TR	5.77 (0.01-2.84)	NA

Table S10.

Survival rates (1-year, 3-year and 5-year) for lesion (≤ 5cm) treatment comparisons estimated by direct, indirect and network meta-analysis in all studies.

Intervention	OR (95%CI)	
	Network Meta-regression	Pairwise Meta-analysis
1-year OS rate for treatment vs reference		
RFA vs RES	0.68 (0.35-1.17)	0.99 (0.95-1.04)
MWA vs RES	0.70 (0.29-1.39)	0.97 (0.77-1.23)
TR vs RES	1.72 (0.66-3.70)	1.01 (0.76-1.33)
PEI vs RES	**0.52 (0.24-0.96)**	1.01 (0.74-1.39)
MWA vs RFA	1.04 (0.55-1.76)	1.01 (0.85-1.20)
TR vs RFA	**2.55 (1.20-4.85)**	1.10 (0.85-1.43)
PEI vs RFA	0.77 (0.51-1.10)	0.98 (0.93-1.05)
TR vs MWA	**2.69 (0.99-6.00)**	0.91 (0.70-1.18)
PEI vs MWA	0.81 (0.38-1.51)	NA
PEI vs TR	**0.34 (0.11-0.63)**	NA
3-year OS rate for treatment vs reference		
RFA vs RES	0.63 (0.37-1.01)	**0.96 (0.94-0.98)**
MWA vs RES	0.62 (0.32-1.09)	0.94 (0.72-1.22)
TR vs RES	0.97 (0.48-1.79)	0.92(0.68-1.24)
PEI vs RES	0.59 (0.30-1.04)	**0.93 (0.86-1.00)**
MWA vs RFA	0.99 (0.64-1.47)	1.05 (0.86-1.26)
TR vs RFA	1.57 (0.89-2.57)	1.20 (0.90-1.60)
PEI vs RFA	0.94 (0.64-1.34)	0.95 (0.89-1.01)
TR vs MWA	1.65 (0.80-3.03)	NA
PEI vs MWA	0.98 (0.55-1.65)	NA

PEI vs TR	0.64 (0.32-1.16)	NA
5-year OS rate for treatment vs reference		
RFA vs RES	**0.52 (0.29-0.88)**	**0.84 (0.80-0.88)**
MWA vs RES	0.55 (0.25-1.05)	0.93(0.78-1.12)
TR vs RES	0.59 (0.25-1.20)	0.69 (0.34-1.42)
PEI vs RES	**0.45 (0.23-0.82)**	**0.79 (0.73-0.85)**
MWA vs RFA	1.06 (0.64-1.61)	0.97 (0.75-1.25)
TR vs RFA	1.16 (0.54-2.21)	1.30 (0.70-2.41)
PEI vs RFA	0.87 (0.57-1.26)	**0.91 (0.84-0.98)**
TR vs MWA	1.16(0.46-2.46)	NA
PEI vs MWA	0.87 (0.46-1.51)	NA
PEI vs TR	0.84 (0.35-1.74)	NA

OR: odds ratio;

RES: resection;

RFA: radiofrequency ablation;

MWA: microwave ablation;

TR: transcatheter arterial chemoembolization and radiofrequency ablation;

PEI: percutaneous ethanol injection;

NA: not available.

Table S11.

Posterior summaries from random effects consistency and inconsistency models for small lesion (<3cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.55	0.21	(0.15-1.00)	0.38	0.23	(0.02-0.88)
τ	12.40	65.04	(1.10-45.68)	109.40	620.40	(1.30-940.00)
resdev	90.04	13.04	(66.16-117.10)	94.65	12.94	(70.06-120.70)

pD	66.48			57.5		
DIC	453.18			404.59		
3-year OS rate for treatment vs reference						
σ	0.59	0.14	(0.34-0.88)	0.6	0.14	(0.36-0.91)
τ	3.26	1.62	(1.34-7.33)	3.28	1.90	(1.19-8.10)
resdev	92.02	14.19	(66.64-122.10)	90.7	13.92	(65.64-120.00)
pD	80.45			71.83		
DIC	589.01			517.44		
5-year OS rate for treatment vs reference						
σ	0.53	0.12	(0.32-0.80)	0.55	0.13	(0.34-0.84)
τ	4.06	2.02	(1.66-8.76)	3.80	2.05	(1.40-8.77)
resdev	63.99	11.47	(43.52-88.24)	63.55	11.37	(43.39-87.90)
pD	64.22			55.07		
DIC	488.23			412.10		

Table S12.

Posterior summaries from random effects consistency and inconsistency models for lesion (3-5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.28	0.25	(0.01-0.92)	0.38	0.34	(0.02-1.28)
τ	3108.00	68630.00	(1.44-4879.00)	19500.00	720600.00	(0.62-4178.00)
resdev	28.90	6.96	(17.25-44.41)	484.70	5117	(0.63-2616)
pD	24.70			24.62		
DIC	166.90			157.30		
3-year OS rate for treatment vs reference						
σ	0.62	0.27	(0.17-1.24)	0.67	0.31	(0.14-1.40)
τ	5.34	12.61	(0.83-21.20)	41.87	585.80	(0.52-77.13)
resdev	32.36	8.17	(18.39-50.07)	32.62	8.22	(18.52-50.51)

pD	30.91			28.63		
DIC	212.30			188.69		
5-year OS rate for treatment vs reference						
σ	0.80	0.46	(0.14-1.94)	0.60	0.42	(0.04-1.64)
τ	337.00	11980	(0.30-20.22)	10100.00	258400.00	(0.37-691.30)
resdev	22.54	6.73	(11.29-37.43)	22.57	6.519	(11.45-36.90)
pD	22.61			19.88		
DIC	146.84			131.53		

Table S13.
Posterior summaries from random effects consistency and inconsistency models for lesion (≤ 5cm) treatment in all studies.

Parameters	Network meta-regression (consistency model)			Inconsistency Model		
	Mean	sd	CI	Mean	sd	CI
1-year OS rate for treatment vs reference						
σ	0.49	0.13	(0.26-0.77)	0.29	0.14	(0.05-0.58)
τ	6.00	6.24	(1.92-16.85)	116.80	1122.00	(2.96-419.40)
resdev	129.2	14.99	(101.40-160)	133.1	14.50	(105.70-162.80)
pD	95.71			78.20		
DIC	692.39			604.18		
3-year OS rate for treatment vs reference						
σ	0.50	0.09	(0.33-0.70)	0.47	0.096	(0.29-0.67)
τ	4.20	1.45	(2.15-7.71)	5.31	2.59	(2.24-11.80)
resdev	124	15.64	(95.16-156.40)	124.5	15.89	(95.35-157.50)
pD	111.54			93.41		
DIC	856.01			723.74		
5-year OS rate for treatment vs reference						
σ	0.44	0.10	(0.26-0.65)	0.44	0.1	(0.26-0.67)
τ	5.30	2.27	(2.38-14.90)	6.09	3.95	(2.29-14.87)

resdev	86.73	13.53	(62.35-115.40)	85.74	13.55	(61.39-114.40)
pD	84.53			68.81		
DIC	670.73			544.40		

sd: standard deviation;

CI: Credible Interval

σ: between-trial standard deviation

τ^2: between-trial variance

resdev: residual deviance

pD: effective number of parameters

DIC: deviance information criterion

Figure S1.

Results of the consistency test for closed loop at 1-year, 3-year, and 5-year survival rate of the lesions < 3 cm, 3-5 cm and ≤ 5 cm.

i Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm ii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm

iii Results of the consistency test for closed loop at 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm

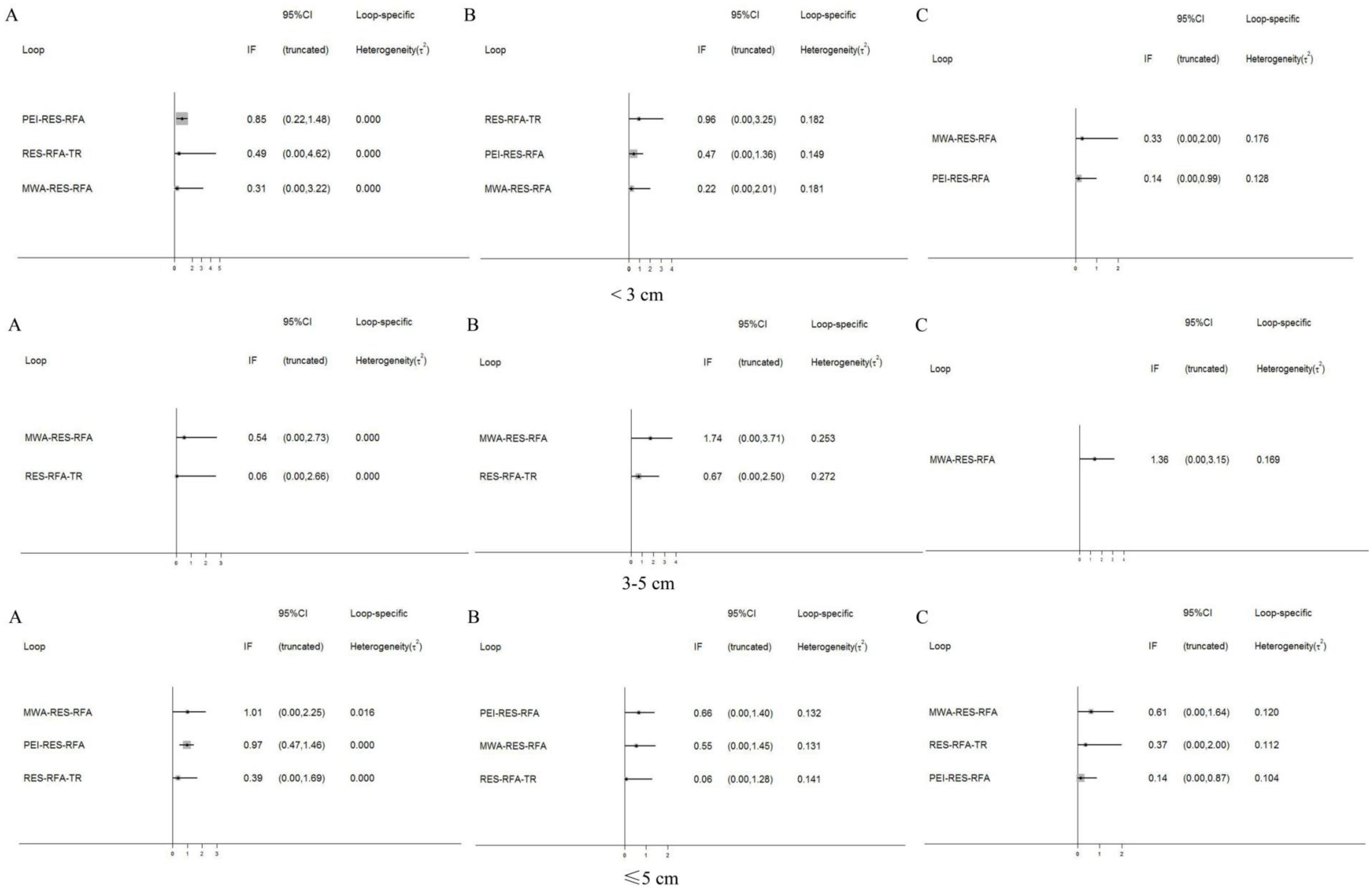

A
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.85 (0.22,1.48) 0.000
RES-RFA-TR 0.49 (0.00,4.62) 0.000
MWA-RES-RFA 0.31 (0.00,3.22) 0.000
B
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
RES-RFA-TR 0.96 (0.00,3.25) 0.182
PEI-RES-RFA 0.47 (0.00,1.36) 0.149
MWA-RES-RFA 0.22 (0.00,2.01) 0.181
C
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.33 (0.00,2.00) 0.176
PEI-RES-RFA 0.14 (0.00,0.99) 0.128
< 3 cm
A
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.54 (0.00,2.73) 0.000
RES-RFA-TR 0.06 (0.00,2.66) 0.000
B
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.74 (0.00,3.71) 0.253
RES-RFA-TR 0.67 (0.00,2.50) 0.272
C
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.36 (0.00,3.15) 0.169
3-5 cm
A
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 1.01 (0.00,2.25) 0.016
PEI-RES-RFA 0.97 (0.47,1.46) 0.000
RES-RFA-TR 0.39 (0.00,1.69) 0.000
B
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
PEI-RES-RFA 0.66 (0.00,1.40) 0.132
MWA-RES-RFA 0.55 (0.00,1.45) 0.131
RES-RFA-TR 0.06 (0.00,1.28) 0.141
C
Loop | IF | 95%CI (truncated) | Loop-specific Heterogeneity(τ^2)
MWA-RES-RFA 0.61 (0.00,1.64) 0.120
RES-RFA-TR 0.37 (0.00,2.00) 0.112
PEI-RES-RFA 0.14 (0.00,0.87) 0.104
≤5 cm

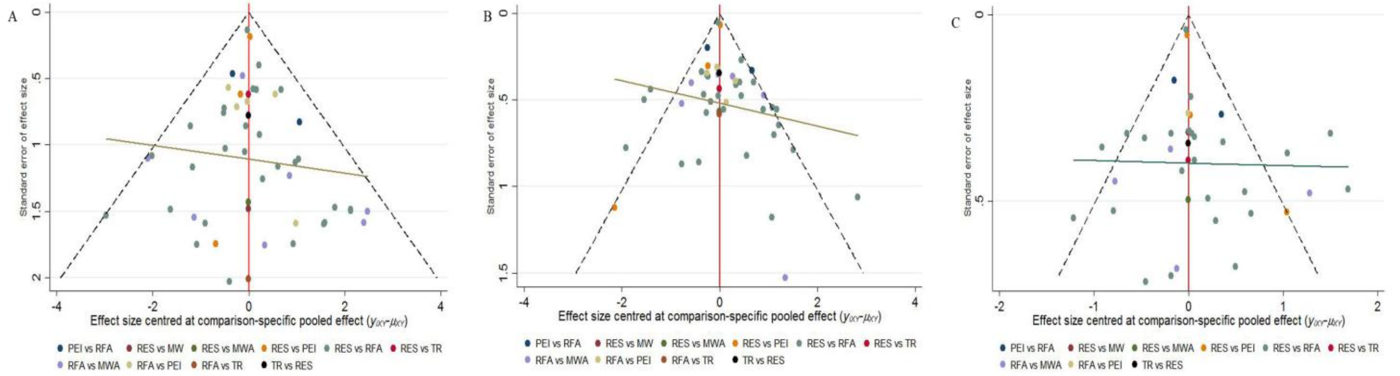
Figure S2.

Assessment of publication bias using funnel plot.

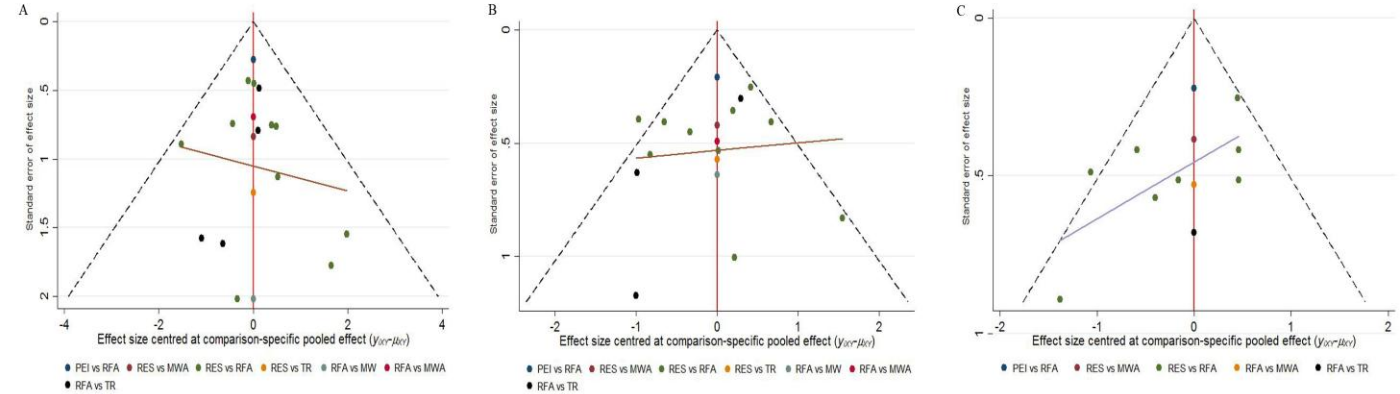
i Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions < 3 cm.

ii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions 3-5 cm.

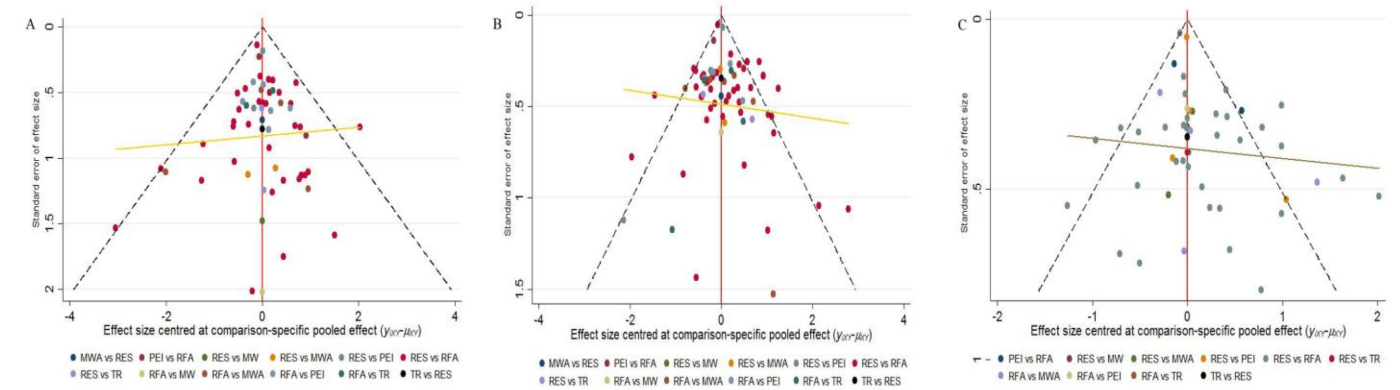
iii Assessment of publication bias using funnel plot for 1-year (A), 3-year (B), and 5-year (C) survival rate of the lesions ≤ 5 cm



i <3cm



ii 3-5cm



iii <5cm

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	5,6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	7,8
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8

METHODS

Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8,9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	9,10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9,10,Figure1, Additional file 1: Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9,10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	11
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11,12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	11,12
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	11,12
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10,11,12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10,11,12
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	11,12

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11,12
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12,13,Figure2-3
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	12,13,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11,12, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	12,13, Figure2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12,13,Figure4-5, Additional file 1: Table S1-S13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	12,13

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12,13, Additional file 1: Figure S1-S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.